CNS Infiltration of Peripheral Immune Cells: D-Day for Neurodegenerative Disease?

Kavon Rezai-Zadeh · David Gate · Terrence Town

Abstract While the central nervous system (CNS) was once thought to be excluded from surveillance by immune cells, a concept known as “immune privilege,” it is now clear that immune responses do occur in the CNS—giving rise to the field of neuroimmunology. These CNS immune responses can be driven by endogenous (glial) and/or exogenous (peripheral leukocyte) sources and can serve either productive or pathological roles. Recent evidence from mouse models supports the notion that infiltration of peripheral monocytes/macrophages limits progression of Alzheimer’s disease pathology and militates against West Nile virus encephalitis. In addition, infiltrating T lymphocytes may help spare neuronal loss in models of amyotrophic lateral sclerosis. On the other hand, CNS leukocyte penetration drives experimental autoimmune encephalomyelitis (a mouse model for the human demyelinating disease multiple sclerosis) and may also be pathological in both Parkinson’s disease and human immunodeficiency virus encephalitis. A critical understanding of the cellular and molecular mechanisms responsible for trafficking of immune cells from the periphery into the diseased CNS will be key to target these cells for therapeutic intervention in neurodegenerative diseases, thereby allowing neuroregenerative processes to ensue.

Keywords brain · central nervous system · neuroinflammation · neuroimmunology · leukocyte · lymphocyte · regulatory T cell · monocyte · macrophage · cytokine · chemokine · transforming growth factor · tumor necrosis factor · interleukin-17 · interleukin-23 · Alzheimer’s disease · Parkinson’s disease · West Nile encephalitis · multiple sclerosis · experimental autoimmune encephalomyelitis · human immunodeficiency virus · amyotrophic lateral sclerosis

Introduction

Certain sites in the body, in particular the central nervous system (CNS), eyes, gonads, and maternal–fetal interface, are known to exhibit limited immunological responses. This phenomenon represents a highly regulated active process that is referred to as immune privilege (Wenkel et al. 2000). As the CNS possesses limited regenerative capacity, it is invariably susceptible to damage mediated by inflammation. Accordingly, immune privilege serves to prevent this damage and to maintain neural health (Galea et al. 2007). While multiple mechanisms contribute to immune privilege, restriction of peripheral leukocyte traffic from the periphery to the CNS is a critically important one. Peripherally migrating and infiltrating leukocytes are tightly regulated at the level of the
blood–brain barrier (BBB) (Engelhardt 2008a). Despite this physical barrier and the brain’s “privileged” immune status, neuroimmune surveillance by peripheral leukocytes does occur, both physiologically and in instances of disease. Our growing appreciation of the brain–immune interface has given rise to the field of neuroimmunology. In this article, we review the implications of CNS immune cell trafficking for the pathoetiology and potential treatment of neurodegenerative diseases.

Both endogenous and exogenous immune responses impact the healthy and diseased CNS. The endogenous brain immune response chiefly consists of brain-resident innate immune cells known as microglia (Streit et al. 2004; Town et al. 2005a). These myeloid cells are traditionally regarded as the resident macrophages of the CNS and are derived from monocyte precursors during embryogenesis (Alliot et al. 1999; Pessac et al. 2001). Microglia form the first line of defense against invading CNS pathogens and are often the first responders to CNS injury. Another endogenous CNS immune responder is the astrocyte, which is a neuroectoderm-derived cell that has limited innate immune properties, including secretion of certain acute-phase reactants and pro-inflammatory cytokines. The term “reactive gliosis” has been used to describe immune activation of glial cells, including microglia and astrocytes, which exist in a quiescent (resting) state in the healthy CNS. Following neural insult, these cells become activated and undergo hypertrophy accompanied by increased expression of cell surface immune antigens. Concomitantly, both activated microglia and astrocytes synthesize and release a myriad of pro-inflammatory cytokines, chemokines, complement proteins, proteinases, and reactive oxygen species. While this neuroinflammatory response may be beneficial for clearing infection and initiating tissue repair mechanisms, if left unresolved, it exposes sensitive neurons to elevated levels of potentially toxic molecules, leading to bystander injury. In fact, there is mounting evidence that chronic neuroinflammation plays a critical role in the pathoetiology of various neurodegenerative diseases including Alzheimer’s disease (AD), multiple sclerosis (MS), and Parkinson’s disease (PD; Town et al. 2005a, b; Akiyama et al. 2000; Kim and Joh 2006; Dheen et al. 2007; Town 2009).

In addition to CNS endogenous immunity, discrete populations of exogenous, peripherally derived immune cells can traffic to the CNS, particularly during disease states. These populations are derived from bone marrow precursors, whereas endogenous microglia are mostly replaced by local CNS progenitors (Eglitis and Mezey 1997; Brazelton et al. 2000; Mezey et al. 2000; Priller et al. 2001; Ajami et al. 2007; Mildner et al. 2007). Peripheral immune cell migration into the CNS resembles typical leukocyte extravasation into other organs, involving stochastic induction of mechanisms governing chemoattraction, cellular rolling, adhesion, and diapedesis across the vascular wall. Yet, infiltration of these cells into the CNS is more complex, owing to the existence of the BBB. Recent reports have furthered our understanding of this unique structure, establishing functionally independent roles as a cellular vs. metabolic barrier (Bechmann et al. 2007).

Recruitment of peripheral immune cells at the level of the BBB is now known to occur primarily at post-capillary venules (Ransohoff et al. 2003). Infiltration at these sites is believed to involve two distinct events: (1) transmigration across the vascular wall into the perivascular space and (2) progression through the glia limitans (a network of astrocyte foot processes) into the brain parenchyma (Owens et al. 2008). Suppression of any one of the mechanisms governing these events may impede brain entry and consequently subvert immune surveillance.

CNS endogenous and exogenous immunity do not function in isolation from one another; rather, there is a dynamic interplay between these two arms. Following microglial and astrocytic activation, chemokines and cytokines released locally diffuse into the bloodstream thereby attracting leukocytes to the site of inflammation and upregulating the expression of cellular adhesion molecules, which are necessary for attachment and transmigration across post-capillary venules (Engelhardt 2008b). Once migrated across the endothelium, leukocytes enter an enlarged perivascular compartment, known as the Virchow–Robin space. It is in this region that leukocytes are “re-stimulated,” maximizing their invasive potential. However, the vast majority of infiltrating peripheral leukocytes are retained in this compartment and do not penetrate the glia limitans, unless they are recruited to the diseased CNS (Bechmann et al. 2007; Ransohoff et al. 2003; Tran et al. 1998).

**Beneficial actions of central nervous system immune cell infiltrates**

Infiltrating monocytes/macrophages as an anti-amyloid force in Alzheimer’s disease

AD is the most common form of dementia, affecting an estimated 5.2 million Americans in 2008, and prevalence is projected to increase to more than 13.2 million by 2050 (Hebert et al. 2003; Plassman et al. 2007). This chronic, progressive neurodegenerative disorder is pathologically earmarked by: (1) deposition of amyloid-beta (Aβ) peptides as β-amyloid plaques, (2) neuronal injury, and (3) low-level, chronic neuroinflammation characterized by activated glial cells (Fig. 1). As first proposed by Hardy and Allsop (1991), the “amyloid cascade” hypothesis purports that mismetabolism and deposition of Aβ peptides as β-amyloid plaques is the principal etiopathological event in
AD, which sets into motion downstream events culminating in neuronal demise. Although neuroinflammation was initially thought to be epiphenomenon, multiple lines of evidence now show that it is directly involved in AD pathogenesis. The most compelling data come from epidemiologic studies showing that exposure to nonsteroidal anti-inflammatory drugs is inversely associated with risk for AD (t’Veld et al. 2001; Szekely et al. 2004, 2007). While microglia are capable of phagocytosing Aβ in vitro, ultrastructural studies in AD patients suggest that these cells are not competent to take up and clear β-amyloid in vivo (Wisniewski et al. 1989, 1991; Frackowiak et al. 1992).

Although AD lacks prominent infiltrates of peripheral leukocytes present in prototypical autoimmune neurodegenerative diseases such as MS (Town et al. 2005b; Aisen 2000), AD patients suffering rare comorbidity of stroke have been shown to exhibit brain-infiltrating macrophages. In early pioneering studies, Wisniewski and colleagues demonstrated that these macrophages contained β-amyloid fibrils (Wisniewski et al. 1991; Frackowiak et al. 1992; Jucker and Heppner 2008), suggesting a productive plaque clearance response mediated by these infiltrating innate immune cells. These findings laid the groundwork for recent studies examining the role of peripheral macrophages in β-amyloid clearance from the brain. Specifically, Jucker and Rivest generated bone marrow chimeras to follow peripheral immune cells in transgenic AD mouse models. Following irradiation of the APP23 AD model mouse line and subsequent transplantation of chimeric bone marrow into these animals, they demonstrated that a small percentage (about 1%) of brain-resident microglia were peripheral recruits, and about 20% of β-amyloid plaques were associated with blood-borne macrophages (Jucker and Heppner 2008; Stalder et al. 2005; Simard et al. 2006).

While these intriguing reports begged the question of whether a relatively small percentage of brain-infiltrating monocytes/macrophages played a functional role in restricting cerebral amyloidosis, recent studies by Ajami and Mildner have suggested that the act of irradiation, by itself, results in BBB damage and leukocyte recruitment to the otherwise normal CNS (Ajami et al. 2007; Mildner et al. 2007). Further, those authors concluded that local microglial cells accounted for the majority of the innate immune response to CNS injury. Thus, (1) the specificity of monocyte/macrophage infiltration in response to CNS disease and (2) the origin—peripheral vs. CNS—resident of these potentially neurodegenerative disease-limiting macrophages/microglia is somewhat controversial.

Even so, Mildner and colleagues observed mainly chemokine receptor CCR2+ monocytes/macrophages populating CNS sites after irradiation (2007). This observation becomes important when considering a study from El Khoury and colleagues, who crossed an AD mouse model with animals deficient in CCR2, thereby interrupting brain recruitment of peripheral monocytes. These bigenic mice had markedly diminished infiltrates of microglia/macrophages near β-amyloid plaques and demonstrated heavier brain amyloid burden than parental AD model mice (El Khoury et al. 2007). Butovsky and colleagues (2007) took a different approach and selectively ablated dendritic-like innate immune cells by systemic injection of diphtheria toxin in mice genetically engineered to target toxicity to CD11c+ cells. They found that ablation of these CD11c+ cells resulted in greater cerebral amyloid burden, suggesting a normal amyloid clearance role for these immune cells. While these studies suggested that peripheral innate immune cells were an important anti-amyloid force, direct evidence for this was lacking.

Two recent reports provide positive evidence that peripheral monocytes/macrophages can act to restrict β-amyloid plaques. In the first paper (Town et al. 2008), we found that transforming growth factor beta (TGF-β)-Smad 2/3 signaling in innate immune cells serves the maladaptive role of suppressing brain infiltration of peripheral monocytes/macrophages. TGF-β, a pleiotropic polypeptide cytokine, plays a pivotal role in immune suppression and functions to maintain an “immune privileged” environment in the CNS. This is particularly apparent in conditions of neurodegenerative disease such as AD, where TGF-β1 mRNA has been shown to be increased by approximately 3-fold vs. nondemented control brains (Wyss-Coray et al. 1997, 2001). Importantly, genetic blockade of TGF-β-Smad 2/3 signaling in innate immune cells of AD model mice mitigates AD-like pathology, including cerebral amyloidosis and brain inflammation. In this model, TGF-
β-Smad 2/3 blockade occurs at the level of peripheral macrophages (and not in brain-resident microglia), resulting in their brain entry (Fig. 2) and clearance of β-amyloid. Thus, it seems that removing an immunosuppressive TGF-β signal to peripheral macrophages “sensitizes” these cells to enter into the brain, where they take up a professional phagocyte role to clear β-amyloid deposits. Importantly, this beneficial anti-amyloid effect does not come at the cost of increased brain inflammation, as these peripheral macrophage immigrants (1) display a CD45+CD11b+Ly-6C cell surface phenotype known to mark “anti-inflammatory” macrophages (Geissmann et al. 2003) and (2) occur in association with increased anti-inflammatory interleukin (IL)-10 levels in brains of Tg2576 AD model mice crossed with mice deficient in TGF-β1. This beneficial anti-amyloid effect does not come at the cost of increased brain inflammation, as these peripheral macrophage immigrants (1) display a CD45+CD11b+Ly-6C cell surface phenotype known to mark “anti-inflammatory” macrophages (Geissmann et al. 2003) and (2) occur in association with increased anti-inflammatory interleukin (IL)-10 levels in brains of Tg2576 AD model mice crossed with mice deficient in TGF-β1. In one model, they administered liposome-encapsulated clodronate, an intra-cellular toxin, to the TgCRND8 mouse model of AD in order to deplete perivascular macrophages. Using this approach, they showed that removal of perivascular macrophages was associated with significantly (~5-fold) increased CAA pathology in AD model mice. In a second set of experiments, the authors stimulated perivascular macrophage turnover by administering chitin to TgCRND8 mice. They noted an approximate 3-fold reduction in thioflavin-S positive β-amyloid deposits in cerebral vessels using this experimental approach. Thus, perivascular macrophages (likely of peripheral origin) represent a unique macrophage subset capable of restricting vascular β-amyloid deposits.

Brain recruitment of leukocytes in West Nile virus encephalitis limits infection

West Nile virus (WNV) is a mosquito-transmitted single-stranded RNA virus that is the most common cause of epidemic viral encephalitis in North America and has recently become a pandemic (Campbell et al. 2002; DeBiasi and Tyler 2006; Gould and Fikrig 2004; Gubler 2007). WNV is both neurotrophic (capable of infecting neurons) and neurovirulent (damaging to the CNS); yet, most infections in humans are asymptomatic, while the elderly and immunocompromised are particularly at risk for life-threatening brain disease, including meningitis and encephalitis (Campbell et al. 2002; Davis et al. 2006). In the mouse model of lethal WNV encephalitis, animals first develop systemic infection, and WNV then crosses the BBB, culminating in encephalitis and ultimately death within weeks (Wang et al. 2001, 2004). During the initial systemic phase of WNV infection, antiviral immune responses including induction of type I interferons (Anderson and Rahal 2002; Brinton 2001; Gilfoy and Mason 2007), humoral immunity (Diamond et al. 2003a, b), and cellular immunity including γδ T cells (Wang et al. 2003a), CD4+ T cells (Kulkarni et al. 1991; Sitati and Diamond 2006), and CD8+ T cells (Shrestha and Diamond 2004, 2007; Shrestha et al. 2006; Sitati et al. 2007; Wang et al. 2003b) serve to limit viral infectivity. After establishing a replicative pool in the periphery, WNV migrates into the CNS, usually 4–7 days after infection (Wang et al. 2004; Diamond et al. 2003a, b). Viral CNS penetration typically coincides with encephalitis, characterized by CNS entry of macrophages, CD4+ T cells, CD8+ T cells, natural killer T cells, and dendritic cells (Glass et al. 2005; Fig. 3a). However, it was previously unclear whether CNS infiltration of leukocytes played a deleterious or beneficial role in lethal WNV encephalitis. Glass and coworkers (2005) found that CNS expression of the chemokine receptor CCR5 and its ligand CCL5 were increased following WNV infection of wild-type mice, and this was associated with infiltration of peripheral leukocytes including CD4+ and CD8+ T cells, natural killer cells, and macrophages bearing the CCR5 receptor. These authors undertook a genetic approach to infect CCR5-deficient mice vs. wild-type animals with WNV, and they found that CCR5-deficient animals were more susceptible to lethal WNV encephalitis, had increased brain viral burden, and had markedly reduced brain leukocyte traffic compared to their wild-type counterparts. Interestingly, these authors were able to reverse this pathogenic CCR5-deficient phenotype by adoptively transferring CCR5 wild-
type spleen cells into CCR5-deficient mice (Glass et al. 2005). In a related report, McCandless and colleagues (2008) examined brain tissues from mice or humans with WNV encephalitis for expression of the chemokine CXCL12 and its receptor, CXCR4. A prior study in mice showed that expression of CXCL12 at the BBB retained infiltrating monocytes within the perivascular spaces of the CNS microvasculature, thereby limiting monocyte entry into the CNS parenchyma (McCandless et al. 2006). They found a reduction in CXCL12 expression and an increase in CXCR4 levels in WNV-infected brains. To determine whether increased CXCR4 levels following WNV encephalitis restricted CNS leukocyte traffic and thereby promoted viral infectivity, these authors treated mice with a CXCR4 antagonist beginning at the time of WNV infection. They noted increased survival in treated mice following infection that was associated with enhanced migration of WNV-specific CD8+ T cells into the brain parenchyma, which likely neutralized the virus (McCandless et al. 2008).

It is interesting that most WNV infection in humans is asymptomatic (Campbell et al. 2002; Davis et al. 2006), underscoring that host immune mechanisms must be in place to suppress WNV infection. We hypothesized that Toll-like receptor 7 (Tlr7), a phylogenetically conserved, germline-encoded pattern recognition receptor that plays a key role in initiating innate immune responses to single-stranded RNA (Qureshi and Medzhitov 2003; Yamamoto et al. 2004; Lund et al. 2004), may serve to limit WNV infectivity. To test this hypothesis, we infected Tlr7-deficient mice with a dose of WNV at which 50% of wild-type mice succumb to mortality (LD50) and found that 91% of Tlr7-deficient mice died. Similarly, infection of MyD88-deficient mice (which lack Tlr7-mediated innate immune responses) with the same dose of WNV resulted in 85% mortality. Both Tlr7- and MyD88-deficient mice had increased viral burden in the blood, brain, and spleen, and while Tlr7-deficient animals manifested increased systemic levels of pro-inflammatory innate immune cytokines, they had reduced abundance of IL-12/23 mRNA both systemically and in the brain. These effects occurred with reduced homing and infiltration of CD45+ leukocytes and CD11b+ monocytes/macrophages into brains of both Tlr7- (Fig. 3b) and MyD88-deficient mice, despite increased brain viral burden in these knockouts. These data led us to hypothesize that WNV-induced, Tlr7-dependent IL-12 or IL-23 production in the CNS might serve to recruit peripheral monocytes/macrophages to neutralize the virus. Several lines of evidence support this notion: (1) IL-23, but not IL-12, was able to directly induce macrophage chemotaxis in an in vitro migration assay, (2) Tlr7-deficient macrophages had reduced abundance of the shared IL-12/23 receptor subunit (IL-12Rβ1) and failed to home to IL-23 in vitro, and (3) mice-deficient in IL-23, but not IL-12, phenocopied Tlr7 and MyD88 knockouts on reduced survival and leukocyte infiltration and homing to the CNS after challenge with lethal WNV encephalitis (Town et al. 2009; Finberg and Wang 2009; van Ooj 2009). Thus, a model emerges where microglia first detect CNS-invading WNV by using Tlr7 to sense viral single-stranded RNA. By signaling through MyD88, microglial cells then secrete high levels of IL-23, which attracts infiltrating monocytes/macrophages and other leukocytes to the CNS, where they function to neutralize the virus.

West Nile virus “Aikido”: using host innate immunity against the host

While the above evidence clearly implicates CNS leukocyte infiltrates as beneficial in the host’s fight against lethal WNV encephalitis, just as in the Japanese martial art “Aikido,” the virus has evolved an elegant form of defense against host innate immunity. We hypothesized that Tlr3, an innate immune pattern recognition receptor that recognizes viral double-stranded RNA (Alexopoulou et al. 2001; Town et al. 2006), may function to militate against WNV infectivity. As a positive single-stranded RNA virus, WNV produces double-stranded RNA during its life cycle, and we predicted that Tlr3-deficient mice would fail to mount an innate immune response to the virus and thus be more susceptible to lethal encephalitis. Strikingly, these knockout mice were resistant (40% survival) to a dose of WNV at which 0% of wild-type mice survived (LD100). Interestingly, Tlr3-deficient mice had increased viral load in the circulation but reduced production of innate immune cytokines including IL-6 and tumor necrosis factor-alpha (TNF-α) versus wild-type counterparts. In parallel, Tlr3 knockouts had reduced viral burden and inflammatory pathology in the brain after WNV infection, and they also showed markedly reduced neuronal pathology and a strikingly intact BBB compared with wild-type mice. It is well known that certain innate immune cytokines, including IL-6 and TNF-α, are able to “permeabilize” the BBB when produced systemically at high levels. To test whether IL-6 or TNF-α responses to WNV infection might act in this way, we infected IL-6- or TNF-α receptor-I-deficient mice with WNV and monitored animals for mortality and BBB compromise. While we did not detect a difference between IL-6-deficient and wild-type control mice, TNF-α receptor I knockouts demonstrated significantly reduced mortality after LD100 WNV challenge associated with reduced leakiness of the BBB (Wang et al. 2004; Diamond and Klein 2004). Thus, while CNS entry of activated leukocytes is a critical host defense mechanism against WNV, the virus has evolved to combat host immunity by using the host’s own systemic pro-inflammatory cytokine.
response to open the BBB in order to gain access to and infect neurons.

Neuroprotective role of peripheral T cell infiltrates in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, ultimately fatal neuromuscular disease pathologically characterized by degeneration of neurons in the motor cortex, brain stem, and spinal cord (Rowland and Shneider 2001). This primarily late-onset neurodegenerative disease affects an estimated 20,000 Americans, and ~5–10% of these cases are purely heritable forms of the disease (Wijesekera and Leigh 2009). Although the mechanisms underlying motor neuron loss are not completely understood, genetic
models of ALS have implicated free radical damage, gliosis, and excitotoxicity as disease-propagating factors (Pasinelli and Brown 2006). The role of the peripheral immune system—specifically infiltrating T cells—in the pathoetiologic neuroinflammatory component of ALS has only recently been examined. Initial reports suggested that the presence of these autoreactive T cells may be epiphenomenon or represent a secondary response with minor deleterious immune effects following neuronal injury (Holmoy 2008).

However, two recent independent reports suggest the converse: that a secondary T cell response may actually be beneficial in the context of ALS. In the first study by Beers and coworkers, ALS model mice expressing mutant copper–zinc superoxide dismutase (SOD1), the most common mutation linked to familial ALS, were crossed with recombination activating gene-2 deficient mice, which lack functional T cells and B cells. Similarly, Chiu and colleagues suppressed T-cell-mediated adaptive immune responses in ALS model mice by crossing SOD1 mutant animals with T-cell receptor β-chain deficient mice, which lack thymocyte development. Interestingly, both bigenic strains in these studies evidenced reduced microgliosis and accelerated rates of neurodegeneration (Beers et al. 2008; Chiu et al. 2008). Thus, these studies suggest that infiltrating CD4+ T cells in particular may confer neuroprotection by shifting the trophic/cytotoxic balance of glia in favor of the former. Interestingly, it was previously shown that (presumed infiltrating) DCs and the chemokine monocyte chemoattractant protein 1 were increased in spinal cord tissue from ALS patients and in the mutant SOD1 mouse model of ALS (Henkel et al. 2004, 2006). It is unclear whether these types of innate immune responses are protective or deleterious in ALS. Yet, combined evidence from the above studies can be interpreted as supporting the notion that promoting productive dialog between the adaptive and innate arms of the immune system via engaging infiltrating CD4+ T cells may militate against ALS pathology. However, it should be noted that this is a relatively new area of exploration, and we await further confirmation of this hypothesis.

Deleterious effects of central nervous system leukocyte traffic

Auto-aggressive T cells cooperate with antigen-presenting cells to initiate demyelination in multiple sclerosis

MS is the most common CNS autoimmune disorder, affecting over 250,000 Americans and over one million individuals worldwide (Steinman 1996). The clinical symptoms of MS are attributable to inflammatory lesions in CNS white matter regions that frequently lead to blindness, loss of motor control, and sensory dysfunction. The pathology of MS is due to an attack on the CNS by the immune system, resulting in demyelination of neuronal axons. Clinical symptoms manifest due to an inability of nerve cells in the brain and spinal cord to communicate via action potentials that propagate down axon fibers. It had long been presumed that antigens present on myelin-producing cells were protected from the immune system owing to residing in the “immune privileged” CNS. However, myelin-reactive T cells that likely recognize a structurally similar viral antigen (known as “molecular mimicry”) are present in the peripheral blood of normal individuals, suggesting that the pathology of the disease may be due to maladaptive CNS entry of autoimmune T cells (Fujinami and Oldstone 1985; Wucherpfennig and Strominger 1995).

The active lesions of MS are characterized by immune cell infiltrates composed of macrophages, T cells, and B cells (Traugott et al. 1982), although it is widely accepted that CNS invasion of encephalitogenic CD4+ T cells is the key pathoetiologic event in MS. Experimental autoimmune encephalomyelitis (EAE) is the most widely used mouse model of MS and is established by immunizing animals with myelin antigen(s) in the presence of adjuvant and pertussis toxin, resulting in (1) development of autoaggressive T cells, (2) CNS leukocyte infiltration, and (3) demyelination in the brain and particularly the spinal cord (Fujinami and Oldstone 1985). Activation of endogenous brain microglia occurs in both human disease and in the EAE mouse model (Greter et al. 2005). Once activated, it is believed that resident microglia chemoattract peripheral pro-inflammatory T helper type 1 (Th1) cells into the CNS. After infiltrating into the CNS, these cells interact with activated microglia, which serve as antigen-presenting cells (APCs; Greter et al. 2005). The importance of T cell/microglial cell interaction in the immunopathology of EAE is underscored by a report from Heppner and colleagues (2005). The authors generated CD11b-HSVTK transgenic mice, which express herpes simplex thymidine kinase in macrophages and microglia, thereby allowing deletion of these cells following ganciclovir treatment. They definitively showed that abrogation of microglial activation inhibited development and maintenance of inflammatory CNS lesions.

Once infiltrated into the CNS of MS patients or EAE model mice, a key molecular event underlying immunopathology is interaction between the CD40 receptor and its cognate ligand, CD40 ligand (CD40L). Activated Th1 cells express CD40L and interact with CD40-bearing reactive microglia in active MS or EAE lesions (Gerritse et al. 1996; Grewal et al. 1996; Tan et al. 1999; Howard et al. 1999; Becher et al. 2001). Early studies indicated that the interaction between CD40L+ microglia and CD40L+ T cells initiated production of interferon (IFN)-γ by reactive T cells in favor of the former. Interestingly, it was previously shown that (presumed infiltrating) DCs and the chemokine monocyte chemoattractant protein 1 were increased in spinal cord tissue from ALS patients and in the mutant SOD1 mouse model of ALS (Henkel et al. 2004, 2006). It is unclear whether these types of innate immune responses are protective or deleterious in ALS. Yet, combined evidence from the above studies can be interpreted as supporting the notion that promoting productive dialog between the adaptive and innate arms of the immune system via engaging infiltrating CD4+ T cells may militate against ALS pathology. However, it should be noted that this is a relatively new area of exploration, and we await further confirmation of this hypothesis.
cells, which in turn acted as a stimulus for increased expression of CD40 on microglia. This feed-forward mechanism would lead to enhanced production of IFN-γ by activated T cells and TNF-α by reactive microglia, the result of which would be chronic activation of APCs via the CD40 pathway (Tan et al. 1999). This immune interaction is pathogenic, as treatment with anti-CD40L antibody or genetic deficiency in CD40L have both been shown to prevent disease development and reduce disease progression in EAE mice (Gerrits et al. 1996; Grewal et al. 1996; Howard et al. 1999). Further, recent preclinical assessment of therapeutic blocking antibodies against human CD40 in a nonhuman primate model of MS showed efficacy when administered early in disease development as well as after the onset of brain inflammation (‘t Hart et al. 2008). These encouraging results suggest that blockade of the CD40–CD40L immune interaction may be a viable therapeutic approach for MS by opposing pro-inflammatory T-cell activation.

Transfer of an expanded population of myelin-reactive encephalitogenic CD4+ Th1 lymphocytes into naïve recipient mice can also induce EAE. In order to recognize their target, these T cells depend on interaction with APCs expressing self myelin antigen in the context of major histocompatibility complex (MHC) class II. Utilizing a mouse model in which MHC class II expression was restricted to dendritic cells (DCs), Greter and coworkers (2005) demonstrated that DCs are capable of licensing CNS immune invasion. In this system, a population of DCs associated with the meninges and CNS blood vessels permitted encephalitogenic T cells to recognize self-myelin antigen, leading to CNS invasion and subsequent immunopathology. These DCs have been reported in normal human brain and potentially represent an interface between the CNS and the immune system in the context of EAE-type brain inflammation (Matyszak and Perry 1996). Interestingly, TGF-β signaling likely acts as an immunosuppressive signal to DCs, thereby mitigating DC-induced CNS leukocyte infiltration. Specifically, targeted functional inactivation of the TGF-β receptor in DCs results in a high frequency of T cells in the CNS along with increased levels of pro-inflammatory cytokines and acute-phase reactants in EAE mice (Laouar et al. 2008).

In addition to CNS infiltration of CD4+ T cell subsets, CD8+ T cell infiltrates are present during the terminal stage of EAE (Laouar et al. 2008). In early work, Sun and colleagues showed that a CD8+ T cell subset could suppress induction of EAE in Lewis rats, suggesting that these cells were counter-regulatory to encephalitogenic Th1 cells (Sun et al. 1988). However, mice deficient in CD8 show less mortality but a higher frequency of relapse than wild-type animals, suggesting that CD8+ T lymphocytes may contribute as both effectors and regulators in EAE (Koh et al. 1992). While it is generally accepted that MHC class II-bearing APCs and Th cells are the main players in the pathogenesis of MS, new evidence has implicated MHC class I, namely human leukocyte antigen-A3 (HLA-A3) and HLA-A3-restricted CD8+ T cells in the pathogenesis of MS (Friese et al. 2008). These results provide a molecular mechanism for the contribution of CD8+ T cells to the pathogenesis of EAE and MS, as interaction between CD8+ T cells and APCs bearing MHC class I molecules reveals a complex network of MHC interactions that may contribute to onset of EAE and MS. The description of myelin-derived peptides that are MHC class I restricted and recognized by CD8+ T cells represents a new avenue toward exploration of the role of CD8+ T cells in demyelinating diseases.

Interleukin-12 versus Interleukin-23 and Interleukin-17 in the pathogenesis of demyelinating disease

IL-12 plays a dominant role in orchestrating differentiation of Th1 effectors and mediating Th1-associated autoimmune diseases (Adorini 1999; Adorini et al. 1997). IL-12 is a heterodimeric protein (known as p70) secreted predominantly by activated APCs and consists of a pair of disulfide-linked subunits designated p40 and p35 (Becher et al. 2002). However, the “common chain” p40 subunit of IL-12 is shared with another heterodimeric cytokine, IL-23, which is comprised of p40 and p19 subunits (Oppmann et al. 2000). This sharing of the p40 subunit between full-length IL-12 and IL-23 heterodimers has made it difficult to determine the specific contribution of these cytokines to MS and EAE. However, using gene-targeting approaches, Becher and colleagues (2002) demonstrated that mice deficient in the p35 subunit of IL-12 were susceptible while p40 null mice were resistant to EAE. In a later complementary study, Cua and coworkers (2003) demonstrated that mice specifically lacking IL-23, and not IL-12, were resistant to EAE. These authors found that the interaction between IL-23-producing CNS DCs and T cells regulates encephalitogenicity during the effector phase of EAE (Cua et al. 2003). When taken together, these studies strongly implicate IL-23—and not IL-12—in EAE immunopathogenesis.

There is also mounting evidence supporting the role of IL-23 in the immunopathogenesis of MS. For example, IL-23 expression is elevated in DCs from MS patients compared to healthy donors (Vaknin-Dembinsky et al. 2006). Furthermore, IL-23 promotes expression of the cytokine IL-17, resulting in differentiation of CD4+ T helper 17 (Th17) effector cells from naïve T cells (Luger et al. 2008). Th17 lymphocytes are capable of transmigrating across BBB endothelial cells expressing IL-17 and are now regarded as a pathogenic T cell in MS due to their ability to functionally interact with and recruit multiple pathogenic...
leukocyte subsets to the CNS, including DCs and CD4+ lymphocytes (Ifergan et al. 2008; Kebir et al. 2007). Yet, it is now generally thought that Th1 and Th17 lymphocyte subsets are independently capable of inducing CNS autoimmune disease (Steinman 2008). However, there likely exists a complicated paradigm where APCs producing IL-23 and other T-cell polarizing cytokines promote Th1 and Th17 effector responses, resulting in CNS trafficking of multiple autoaggressive leukocyte subsets.

Role of peripheral immune cell infiltrates in Parkinson's disease

PD is the most common movement disorder, affecting over one million Americans and over four million individuals worldwide (Dorsey et al. 2007). After AD, it is the next most common progressive neurodegenerative disorder affecting elderly individuals over 65 years of age (Dorsey et al. 2007). Pathologically, PD is characterized by: (1) preferential loss of dopaminergic neurons, (2) the presence of Lewy bodies (cytoplasmic inclusions composed principally of abnormal α-synuclein), and (3) reactive gliosis. These three pathological hallmarks all occur within a small region of the midbrain known as the substantia nigra pars compacta (SNpc). While genetic and pharmacologic models of the disease have established oxidative stress, mitochondrial, and proteosomal dysfunction as disease-perpetrating events, the mechanism mediating dopaminergic deficit in sporadic PD remains unknown (Dauer and Przedborski 2003). The search for a PD pathoetiologic mechanism has uncovered the immune system—particularly innate neuro-inflammatory responses—as a potential candidate (Czlonkowska et al. 2002; Whitton 2007). In addition, recent reports have also implicated the adaptive immune system in PD pathogenesis.

Although PD is not generally considered an autoimmune disease, a recent study by Benner and colleagues (2008) demonstrated that modified “self” epitopes such as nitrated α-synuclein (N-α-Syn) can overcome immunological tolerance and activate peripheral leukocytes in cervical lymph nodes following administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to wild-type mice. In addition, adoptive transfer of T cells from syngeneic donors immunized with N-α-Syn exacerbated dopaminergic neuronal loss following exposure to MPTP. Importantly, these purified CD3+ populations of T cells were capable of trafficking to and infiltrating the SNpc (Benner et al. 2008). In accordance with these findings and those of the seminal work of McGeer and coworkers (1988), Brochard and colleagues (2009) reported that T cells are largely recruited to the SNpc in the brains of patients with PD. These brain-invading lymphocytes consisted of a heterogeneous population of both CD8+ and CD4+ cells. A similar profile of peripheral leukocyte infiltration was also present in MPTP mouse models of PD, further validating the relevance of the model to the human syndrome (Brochard et al. 2009). Interestingly, both this experimental model and the clinical syndrome exhibit BBB dysfunction (Kortekaas et al. 2005). However, it should be noted that while the BBB appears to be “leaky” following exposure to MPTP, it is unlikely that this phenomenon is sufficient to grant peripheral leukocytes direct access to the diseased brain. Rather, a dysfunctional BBB is likely one of many steps involved in recruitment of peripheral immune cells to the PD brain.

To ascertain which T cell subsets might contribute to PD pathogenesis, Brochard and colleagues (2009) went on to examine dopaminergic neuronal loss in mice deficient in one or both subsets of T cells following MPTP intoxication. Interestingly, mice lacking complete cell-mediated immunity or CD4+, but not CD8+, T cells were protected against MPTP-induced injury, suggesting a pathogenic role of CD4+ T cells in the MPTP mouse model of PD. Upon further elucidation of this pathogenic role, CD4+ T cells were found to arbitrate dopaminergic neuronal loss via a Fas/FasL-dependent mechanism (Brochard et al. 2009). In addition, a recent report by Reynolds and colleagues further substantiated the detrimental activities of CD4+/CD25+ cells by demonstrating the ability of these effector T cells to exacerbate microgliosis following exposure to N-α-Syn. This study also examined the potentially beneficial activities of infiltrating CD4+/CD25+ regulatory T cells (Tregs). These CNS infiltrating Tregs were capable of suppressing microgliosis by secreting cytokines that mitigate inflammatory responses or by directly inducing microglial apoptosis via a similar Fas/FasL-dependent mechanism as described above (Reynolds et al. 2009). While studies investigating the role of Tregs in PD have not definitively established protective vs. deleterious activities at various stages during disease, it is likely that the Treg lymphocyte subset has the potential to be mobilized to abrogate PD pathology (Reynolds et al. 2007, 2009). Taken together, these results suggest the existence of highly regulated, adaptive immunopathogenic mechanisms at work in PD that may ultimately be harnessed as therapeutic(s).

Detrimental role of peripheral immune cell infiltrates in HIV-associated neurocognitive dysfunction

Neurological disease arising from human immunodeficiency virus (HIV) remains a frequent complication of this viral infection. Specifically, HIV-associated neurocognitive dysfunction (HAND), which in itself is comprised of a spectrum of neurological impairments, continues to plague patients with advanced HIV infection despite the advent of highly active antiretroviral therapy (Ghafouri et al. 2006; Reger et al.
Although the pathological mechanisms responsible for HAND are unclear, an abundance of clinical and laboratory investigations suggest that HIV encephalitis (HIVE), advancing age, and even comorbid neurodegenerative disease may interact in an additive or synergistic manner resulting in the clinical phenotype of this disorder (Ghafouri et al. 2006; Gonzalez-Scarano and Martin-Garcia 2005). It is well known that peripheral HIV-infected monocytes/macrophages infiltrate the CNS, resulting in reactive gliosis, formation of multinucleated giant cells, and neuronal loss characteristic of HIVE (Ghafouri et al. 2006; Gonzalez-Scarano and Martin-Garcia 2005; Budka 1991). However, the role of invading T-cell populations in HIVE-mediated neurodegeneration has only recently been investigated.

Two studies by Petito and coworkers examined infiltrating T lymphocytes in the brains of end-stage-acquired immunodeficiency syndrome (AIDS) patients with and without HIVE. In their earlier work, they found that hippocampal effector/memory CD45RO+ T lymphocytes were significantly increased in individuals with HIVE. Interestingly, these CD4+ and CD8+ T cells were observed in direct contact with neurons, underscoring the potential for lymphocyte-mediated neuronal injury or possibly trans-receptor-mediated neuronal infection (Petito et al. 2003). In their follow-up report, these authors observed cytotoxic CD8+ T cells in the parenchyma of AIDS patients with HIVE. The perineuronal localization of these T cells and their associated cytotoxic granules again suggested T lymphocyte-mediated neuronal killing (Petito et al. 2006).

As indirect evidence of this pathogenic mechanism, Liu and colleagues demonstrated that adoptive transfer of Tregs attenuated reactive gliosis, viral replication, and neuronal loss in an HIVE mouse model. Importantly, adoptive transfer of effector T cells in this model had contrary effects (Liu et al. 2009). Although it is generally accepted that Tregs suppress antiviral immune responses in the periphery, it is likely that these same responses may directly or indirectly target neurons and even exacerbate HIV dissemination in the CNS. Therefore, specifically gating the subsets of T lymphocytes that are granted access to the HIV-infected brain may help resolve infection and consequently prevent or treat HAND.

### Concluding remarks

In this review, we have explored both beneficial and deleterious impacts of peripheral immune cell traffic into the CNS depending on disease state. The AD brain responds to pathology by increasing “immune privilege” barriers that restrict CNS leukocyte traffic, including upregulation of TGF-β1 expression. While TGF-β1 is directly neurotrophic (Tesseur et al. 2006), this response may ultimately be maladaptive as it precludes brain entry of peripheral monocytes/macrophages. Overcoming this barrier by blocking innate immune TGF-β-Smad 2/3 signaling results in robust brain entry of peripheral macrophages and restriction of cerebral amyloidosis. In WNV encephalitis,
infiltration of peripheral leukocytes, including CD4+ and CD8+ T cells and monocytes/macrophages, into the CNS also serves a beneficial role to seek out and neutralize the virus, thereby limiting CNS infectivity. However, the host's frontline innate immune defense is also capitalized upon by the virus to permeabilize the BBB, allowing viral entry into the CNS. Thus, aggressive pro-inflammatory innate immune responses must be kept in check to limit WNV infection of the CNS and to minimize neuronal bystander injury. In models of ALS, CD4+ T lymphocytes infiltrate the CNS where they may fine-tune glial responses to promote a neuroprotective microenvironment. In the context of MS and the EAE mouse model, infiltration of autoaggressive leukocytes including Th1 and Th17 CD4+ T cell subsets promotes brain inflammation and associated CNS injury. Thus, the pathology of MS and EAE underscores the importance of restricting “runaway autoimmune” leading to CNS lesions. The role of peripheral leukocyte traffic to the brain is just beginning to be explored in PD, which was classically thought to be a neurodegenerative disease without an immune component. However, CD4+ and CD8+ T cells are detected in PD patient brains, and deletion of CD4+ T cells rescues mice from PD-like effects of MPTP intoxication. Finally, the impact of cytotoxic T-cell infiltration in HAND is viewed with increasing interest, as CD8+ T cells and their cytotoxic granules are present in the brains of late-stage AIDS patients with HIV-related T lymphocyte-mediated neuronal loss.

What emerges from studies reviewed in this article is that peripheral immune responses in the CNS are neither inherently beneficial nor damaging. However, controversy still surrounds whether peripheral immune responses directed toward self-antigen in the CNS are beneficial, a concept known as “autoimmune neuroprotection” or “protective autoimmunity” (Schwartz and Kipnis 2005). A number of recent reports touch on this debate, suggesting that early autoaggressive immune responses may accelerate the pathogenesis of various neurodegenerative diseases (Liu et al. 2009; Reynolds et al. 2009; Planas and Chamorro 2009). These and other studies also find that curbing this response via Treg-mediated immunosuppression affords protection against neurodegeneration, as appears to be the case with EAE, PD and HIV (Liu et al. 2009; Reynolds et al. 2007; Kohm et al. 2002). Conversely, an alternative view suggests that dysregulation of autoaggressive immune responses may allow neurodegenerative mechanisms to persist. This is apparent in studies examining the adverse activities of Tregs in models of viral encephalitis and ALS (Bai et al. 2009; Goldstein et al. 2009). Failure to engage the appropriate immune responses may prevent resolution of neuroinflammation, resulting in a common feature of these neurodegenerative diseases: chronicity. In the final analysis, CNS leukocyte traffic may serve either beneficial or deleterious roles, depending on the brain disease state (Fig. 4). A critical understanding of the cellular and molecular mechanisms responsible for this intriguing and important interface between the CNS and the immune system will likely lead to novel therapeutics in the future.

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