Inflammation and Adaptive Immunity in Parkinson's Disease

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The immune system is designed to protect the host from infection and injury. However, when an adaptive immune response continues unchecked in the brain, the proinflammatory innate microglial response leads to the accumulation of neurotoxins and eventual neurodegeneration. What drives such responses are misfolded and nitrated proteins. Indeed, the antigen in Parkinson's disease (PD) is an aberrant self-protein, although the adaptive immune responses are remarkably similar in a range of diseases. Ingress of lymphocytes and chronic activation of glial cells directly affect neurodegeneration. With this understanding, new therapies aimed at modulating the immune system's response during PD could lead to decreased neuronal loss and improved clinical outcomes for disease.

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting the elderly. Pathologically, the disease is characterized by the cytoplasmic accumulation of proteinaceous aggregates called Lewy bodies (LBs), which are mainly comprised of α-synuclein (α-syn) and ubiquitin (Spillantini et al. 1997, 1998). Progressive degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta and their projections into the caudate nucleus leads to substantial decreases in dopamine levels, which manifest as resting tremor, bradykinesia, rigidity, and gait dysfunction (Dauer and Przedborski 2003). Currently, no curative treatments or treatments that interdict disease progression exist. Although the etiology of PD remains unknown, abundant evidence implicates immune system abnormalities and central nervous system (CNS) inflammation in disease pathobiology (McGeer et al. 1988a; Stone et al. 2009; Kosloski et al. 2010). Harnessing inflammatory responses through targeted modulation of innate and adaptive immune responses has gained increasing interest in recent years as a potential therapeutic strategy. The interplay between innate and adaptive immunity in the pathobiology of PD, the evolution and change in such immune responses, and the means to alter it to the benefit of the diseased, is the focus of this article.

ADAPTIVE IMMUNITY AND THE CNS

William Hickey wrote, "vertebrates possess two bodily systems capable of learning and remembering: the nervous system and the immune system" (Hickey 2001; Weiner 2008). The CNS was once thought to be an "immune privileged"

site, in which immune cells of the periphery could not enter or rarely entered, and thus the two systems had little to no interaction. This hypothesis was supported by the early observation that tissue grafts in the eye or brain survived longer than grafts in other areas of the body (Medawar 1948). However, today, evidence of an interactive adaptive immune system and the CNS abounds. Indeed, communication between the CNS and peripheral immune system is much more fluid than previously considered and, as such, may substantially affect disease progression in neurological disorders (Ferrari and Tarelli 2011). Peripheral immune responses can trigger inflammation and exacerbation of CNS degeneration in several neurodegenerative diseases such as Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), stroke, and prion-mediated diseases (Cunningham et al. 2005a,b; Kamer et al. 2008; Fiala and Veerhuis 2009; Holmes et al. 2009; Lee et al. 2009a; McColl et al. 2009; Reale et al. 2009; Stoll and Bendszus 2009; Teeling and Perry 2009; Heesen et al. 2010; Perry 2010), and particularly PD (Hasegawa et al. 2000; Arai et al. 2006). In those disorders, increasing inflammation and breakdown of the blood–brain barrier (BBB) forces increased communication between the CNS and peripheral immune systems as evidenced in several neurodegenerative diseases with increased leukocyte migration within the brain parenchyma (Stolp and Dziegielewska 2009). Under infectious or inflammatory conditions, peripheral immune cells have relatively unfettered access to the CNS. These immune cells influence neuroinflammation and neurodegeneration not only in a paracrine fashion, but also in an endocrine fashion. In turn, the CNS is capable of influencing the immune response to pathogens in the periphery through the neuroendocrine system. Thus, the immune system is not only charged with protecting the CNS from pathogens and injury, but is also capable of affecting the functions and homeostasis of resident CNS cells, for better or worse. Furthermore, researchers are beginning to harness the neurotrophic effects of the immune system to aid in repair and regeneration in the CNS.

Even under normal conditions, activated T and B lymphocytes patrol the CNS in low numbers, whereas naïve lymphocytes are excluded (Hickey 1999; Togo et al. 2002; Engelhardt and Ransohoff 2005). Although fewer activated T cells infiltrate the normal CNS than other tissues (Yeager et al. 2000), this may be owing to the low level of adhesion molecules expressed on endothelial cells under normal conditions (Hickey 2001), whereas increased expression of adhesion molecules leads to increased lymphocyte infiltration. When cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α are secreted by activated glia in the brain, or are present in circulating blood, permeability of the BBB is increased and the expression of cellular adhesion molecules (such as selectins) on microvascular endothelial cells are up-regulated (Wong et al. 1999). Activated T cells and B cells are then able to extravasate and migrate to the site of neuronal injury in increased numbers (Aloisi et al. 1999; McGeer and McGeer 2003; Olson and Miller 2004).

Indeed, abnormalities in the BBB have been shown where T-cell infiltration occurs in neuro-AIDS (Petito and Cash 1992; Petito et al. 2003), AD (Rogers et al. 1988; Togo et al. 2002; Desai et al. 2007), and PD (Farkas et al. 2000). Furthermore, whereas the CNS lacks a defined lymphatic system, antigens do exit the CNS via arachnoid villi, cranial nerves, and spinal nerve root ganglia to lymph (Cserr and Knopf 1992). Once in the lymph, these antigens may be taken up by dendritic cells, processed, and presented to T and B cells to mobilize an adaptive immune response to the CNS. Whereas acute neuroinflammation is beneficial to regaining homeostasis and normal function of the CNS after injury or infection, chronic neuroinflammation is damaging to the CNS and may initiate or amplify neurodegeneration associated with HIV-1 encephalitis, AD, or PD.

Cross-Regulation of Adaptive and Innate Immunity in the CNS

Innate immunity consists of the immune mechanisms that are encoded in the germline and are possessed at birth, and work in a "nonspecific"

manner, for immediate defense against microbial infection, notably sepsis (Perry 2011; Stearns-Kurosawa et al. 2011). A host's first line of defense consists of physical barriers such as skin- and cell-regulated enzymes used to clear pathogens and debris, and serves to remove foreign substances by phagocytosis, to recruit immune cells to sites of infection, to activate the complement cascade, but most importantly, to process and present antigens for activation of and recognition by the adaptive immune response (Kim 2005; Filias et al. 2011; Sakaguchi 2011; Sly and Holt 2011; Veerhuis et al. 2011). Its conservation is matched only by its simplicity, except for a broad range of self–nonself pattern-recognition receptors. Such immune activation functions are through nonspecific, generic recognition of common cell signaling pathways shared through a host of endogenous and exogenous factors. These pathways are gaining considerable interest in therapeutic development (Goldman 2007; Basith et al. 2011). Cell debris and foreign matter within the CNS engage toll-like receptors (TLRs), which are expressed by microglia, astrocytes, oligodendrocytes, as well as by neurons (Lv et al. 2011; Zurolo et al. 2011). Engagement of TLRs activates signaling cascades that result in proinflammatory cytokine and chemokine production and in effects on the brain directly or indirectly through glial or BBB function (Franklin et al. 2011; Greenwood et al. 2011; Holman et al. 2011; Kacimi et al. 2011).

The innate immune system also is linked to its adaptive arm through the abilities to provide required "signals" for antigen presentation and to act as final effectors by T-cell-mediated responses in the CNS. The interrelationships between innate and adaptive immunity permit the host to recognize environmental and exogenous cues and work in concert to protect and sustain the host. Central to the innate immune network are microglia (Perry 2011). They secrete both anti- and proinflammatory cytokines and chemokines together with other factors that regulate not only adaptive immunity, but also neural function and neural homeostasis. Those microglial factors found in the brain, cerebrospinal fluid (CSF), and peripheral blood include transforming growth factor beta (TGF-β), IL-1 alpha/beta (IL-1α/β), IL-6, IL-10, IL-12, IL-23, and TNF-α, many chemokines (RANTES/CCL5, MCP-1/CCL2, and IP-10/CXCL10), proteolytic enzymes, matrix metalloproteinases, complement, growth factors, and glutamate (Griffin et al. 1989; Dickson et al. 1993; Moore and Thanos 1996; Qiu et al. 1997). Moreover, COX-2 is present as increased levels of TRAF family member-associated NFκB activator (TANK) and NFKB1 in the SN, and IL-15, RANTES, and IL-10 levels are significantly elevated in brains and peripheral circulation in PD patients (Blum-Degen et al. 1995; Teismann et al. 2003; Rentzos et al. 2007, 2009; Reynolds et al. 2008a). Furthermore, innate immunity regulates lymphocyte infiltration into the CNS. Cytokines, such as IL-1β and TNF-α, secreted by activated glia or endothelial cells increase BBB permeability (Desai et al. 2007), and the expression of cellular adhesion molecules (such as E-selectin) on microvascular endothelial cells are up-regulated (Wong et al. 1999), together increase permeability of the BBB and increase homing, extravasation, and activation of lymphocytes.

Of the antiinflammatory cytokines produced by T cells, macrophages, and microglia, TGF-β modulates injurious responses to the brain (Finch et al. 1993) and suppresses proinflammatory microglia and T-cell responses (Sakaguchi 2004), and as such may represent a neuroprotective host response (Chao et al. 1994). However, TGF-β released from the damaged brain microvasculature contributes to inflammation by increasing expression of endothelial IL-1β and TNF-α (Grammas and Ovase 2001). The engagement of TLRs leads to translocation of nuclear factor-κ light-chain enhancer of activated B cells (NF-κB) and AP-1 to the nucleus where they induce transcription of a broad range of innate immune proteins. Once activated, microglia secrete both neurotrophic and neurotoxic factors (Zhang and Fedoroff 1996; Glezer et al. 2007); proinflammatory cytokines including IL-1α, IL-1β, and TNF-α (Giulian et al. 1986; Sawada et al. 1989); and neurotrophins including nerve growth factor (NGF) and neurotrophin 3 (NT-3) (Elkabes

et al. 1996; Heese et al. 1998). However, during chronic inflammation, the neurotoxic effects of microglia are proposed to eventually outcompete the neurotrophic effects, thus increasing neurodegeneration (Rock et al. 2004). In turn, increased inflammation and BBB permeability allow naïve T cells greater entry and accessibility to activated microglia that in the acute phase induce proinflammatory T-cell responses, and can, under chronic conditions, perpetuate the inflammatory state by engaging and activating polarized proinflammatory effector T cells that have expanded in the periphery and ingressed to sites of neurodegeneration.

Induction of Innate and Adaptive Immune Activation by Misfolded Proteins

Evidence abounds for the involvement of misfolded proteins in the pathology of neurodegenerative diseases, as well as in the activation of microglia and antigen-presenting cells (APCs) that function to induce the adaptive immune arm. In PD, LBs are associated with activated microglia and dopaminergic neuronal death. LBs are comprised mostly of α-syn, ubiquitin, and neurofilament (Goldman et al. 1983; Spillantini et al. 1997, 1998; Jellinger 2007) and posttranslationally modified forms of α-syn have an increased propensity to aggregate (Uversky et al. 2005; Cavallarin et al. 2010). These α-syn species are created by ubiquitination (Shimura et al. 2001), phosphorylation (Fujiwara et al. 2002), or oxidation and nitration (Giasson et al. 2000), and are found in LB inclusions, extraneuronally in PD brains (Lee 2008), and in the periphery of PD patients (Beach et al. 2010). Abnormal species of α-syn found in PD patients are also present in LBs of other synucleinopathy-affected brains, including AD and multiple-system atrophy (MSA) (Duda et al. 2000; Giasson et al. 2000; Cavallarin et al. 2010). These observations are supported by in vitro data and animal models of PD in which overexpression of native or mutated forms of α-syn show that aberrant species have an increased propensity to aggregate (Parihar et al. 2009; Koprich et al. 2010). Aggre-

gation of α-syn is also caused by genetic mutations. Although most cases of PD have no family history of disease, point mutations in the gene encoding α-syn (SNCA; OMIM 163890) are linked to autosomal-dominant parkinsonism (PARK1, OMIM 168601) (Polymeropoulos et al. 1996, 1997; Kruger et al. 1998; Zarranz et al. 2004), as are duplications and triplications of the SNCA gene (PARK4, OMIM 605543) (Singleton et al. 2003; Chartier-Harlin et al. 2004), all of which present increased aggregation of α-syn (Narhi et al. 1999; Li et al. 2001; Uversky 2007). Taken together, these observations led to the α-syn burden hypothesis, which posits that sporadic PD results from the inability to clear α-syn, whereas familial PD results from overproduction of normal α-syn, mutations in α-syn that prevent or slow clearance, or mutations in other proteins that normally assist in α-syn clearance (McGeer and McGeer 2008). McGeer further hypothesized that disease can be eliminated with the reduction of α-syn production or prevention of α-syn aggregation. Thus, vaccines currently being developed for PD, target α-syn in order to increase clearance of aggregated and aberrant forms of the protein. However, because evidence supports a nonneuronal cell autonomous theory for PD progression whereby neuroinflammation is strongly implicated (Dawson 2008), immunotherapeutic strategies also incorporate means by which to attenuate the neuroinflammatory component.

Furthermore, reactive oxygen species produced by activated microglia increases nitration of α-syn and neuronal cell death (Shavali et al. 2006); and in turn, immune T cells that recognize nitrated α-syn (N-α-syn) enhance the neurotoxic activities of microglia in the acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of nigrostriatal degeneration (Reynolds et al. 2008b). Activated T cells and B cells are then able to enter the CNS more readily and migrate to the site of neuronal injury (Aloisi et al. 1999; McGeer and McGeer 2003; Olson and Miller 2004). Indeed, increased BBB permeability is found in both AD and PD, allowing for increased lymphocytic ingress (Rogers et al. 1988; Farkas et al. 2000; Togo et al.

2002; Desai et al. 2007). In this way, activated innate immune cells of the CNS can affect the adaptive immune system in the periphery and recruit cells to the CNS. However, another way in which the adaptive immune system may be activated during neurodegeneration is through the escape of CNS proteins into the periphery. Indeed, aberrant species of disease-specific proteins, including phosphorylated α-syn, are present in tissues outside the CNS in PD patients (Beach et al. 2010). The occurrence of these aberrant forms of α-syn in the periphery, such as the gastrointestinal tract and draining cervical lymph nodes, presents a possible means for exposure to the protein and subsequent activation of the adaptive immune system.

ADAPTIVE IMMUNITY IN PD

From an earlier *Perspectives in Biology and Medicine* (Johns Hopkins University Press), Abramsky and colleagues broached the possibility that PD may arise from autoimmune blockade of striatal dopamine receptor function (Abramsky and Litvin 1978). Although clinical evidence has not sufficiently supported this possibility, many studies have implicated the adaptive immune system in PD progression. With high glia/neuron ratios of 3:1 in the brain (Lawson et al. 1990) and the density of microglia contained within the SN, the highest of any region in the brain (Kim et al. 2000), any increase in the inflammatory status of the patient may additively, if not synergistically amplify neuroinflammation. Since 1988, when McGeer and colleagues found HLA-DR-positive (activated) microglia phagocytosing-free neuromelanin in post mortem PD SN (McGeer et al. 1988a), activated microglial consistently have been observed in PD patients, whereas others have shown higher expression levels of polymorphic major histocompatibility complex (MHC) class II (MHC II) molecules, HLA-DR and HLA-DQ, expressed by monocytes in the CSF and peripheral blood of PD patients compared with controls (McGeer et al. 1988b; Fiszer et al. 1994a; Lampe et al. 2003). More recently, genome-wide association studies (GWASs) of PD patients (Hamza et al. 2010; Saiki et al.

2010; Nalls et al. 2011; Puschmann et al. 2011; Simon-Sanchez et al. 2011), including a meta-analysis of the GWASs (Nalls et al. 2011), verified an increased relative risk for PD and expression of HLA-DR or HLA-DQ MHC II molecules, leading to the designation of HLA-DRA as PARK18 (Hamza et al. 2010). Increased susceptibility to PD owing to MHC II molecules could reflect increased neuroinflammation associated with up-regulation of those molecules or alternatively, could represent immune responses to self- or weak nonself-antigens. Activated microglia and monocytes in PD brains and CFS secrete proinflammatory and neurotoxic cytokines and chemokines that disrupt the BBB and attract lymphocytes to the site of neuronal injury. Indeed, levels of IL-1β, IL-6, and TNF-α are elevated in the CFS of PD patients (Blum-Degen et al. 1995; Gonzalez-Scarano and Baltuch 1999), and intercellular adhesion molecule-1 (ICAM-1)-positive glia are also increased in the SN of PD brains (Miklossy et al. 2006). Together, these data support the hypothesis that activation of cells of the innate immune system, such as microglia and monocytes, directly contribute to the pathobiology of PD. Furthermore, it has been shown that these cells are activated by overexpression of α-syn or aberrant forms of α-syn. Aberrant posttranslational modifications of α-syn, such as nitration (N-α-syn), can be found in LB inclusions of PD brains (Giasson et al. 2000) and cause the protein to aggregate more readily (Uversky et al. 2005). Aggregated α-syn activates microglia (Zhang et al. 2005), which have been shown to produce nitric oxide and superoxide in mice and inducible nitric oxide synthase (iNOS) in humans, which increases nitration of α-syn and perpetuates the proinflammatory innate immune response in PD (Fig. 1) (Hunot et al. 1996; Gao et al. 2008). Nitrated α-syn in turn amplifies activation of microglia and antigen-presenting cells that correspondingly up-regulate both humoral and cell-mediated responses to nitrated α-syn in the MPTP model (Benner et al. 2008).

Although autoantibodies against dopamine neuron antigens are present in sera and CSF of PD patients (McRae-Degueurce et al. 1988;
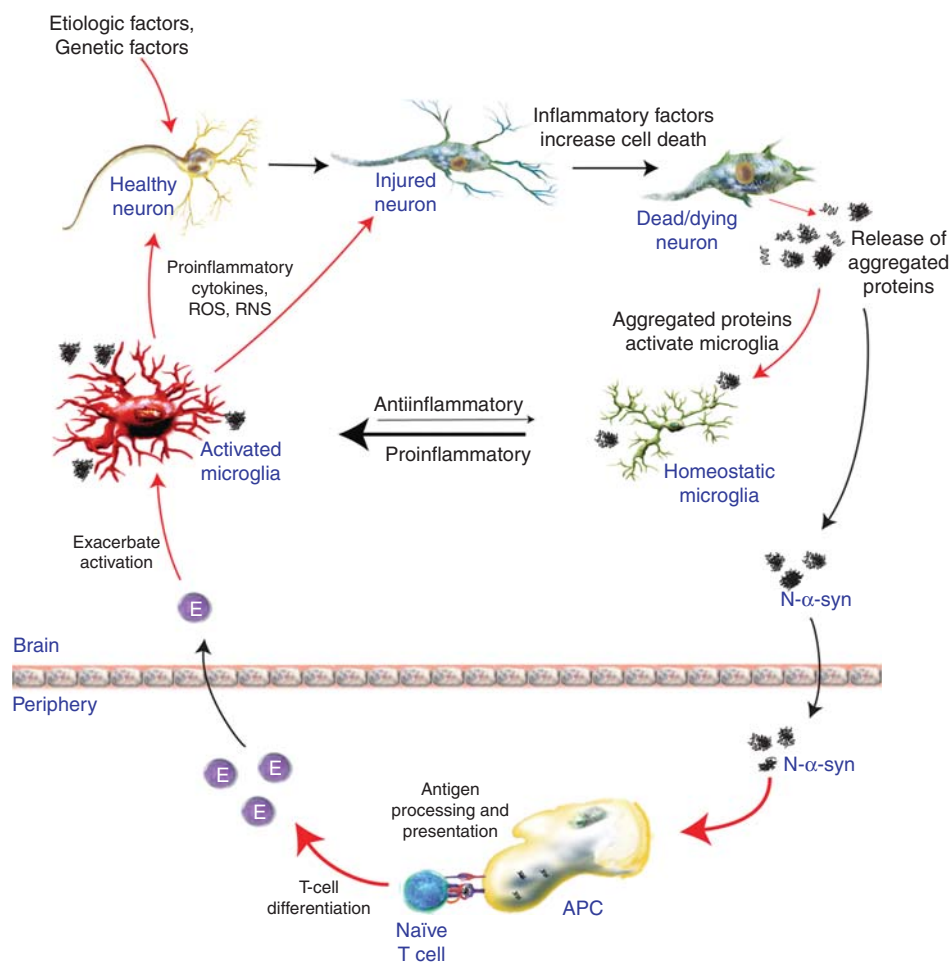
Figure 1. Immune contributions to PD pathogenesis. Reactive microgliosis is a prominent feature of neurodegenerative diseases such as PD. Microglia are sensitive to changes in their microenvironment, which include factors released from damaged/dying neurons such as modified and aggregated proteins (i.e., α-synuclein found in Lewy bodies). Activated microglia may respond to these factors by secreting proinflammatory factors and ROS/RNS that perpetuate neuronal injury and death. Furthermore, modified α-synuclein (e.g., N-α-synunclein) may drain to the periphery where an adaptive immune response is mounted against these antigens. Although increased numbers of lymphocytes are found in the SN of PD patients' brains, their exact role is not yet known. However, experimental evidence suggests that effector T-cell (E) responses contribute to microglia activation and accelerate neurodegeneration. Taken together, the innate and adaptive immune responses operative in PD may accelerate neurodegeneration and are an active area of research.

Dahlstrom et al. 1990; Kunas et al. 1995), the role of the humoral adaptive immune system has only recently begun to be investigated in depth. In addition to a variety of antibodies directed against globally expressed tissue antigens such as heat shock protein (HSP)-65 and HSP-70 (Fiszer et al. 1996), PD patients also show brain-associated autoantibodies including those directed against, GM1, S100B, glial fibrillar acidic protein (GFAP), NGF, neurofilament, myelin basic protein, tau, Aβ, and neuronal calcium channels, as well as α-syn and its modified and fibriliary forms (Elizan et al. 1983; Karcher et al. 1986; Appel et al. 1994;

Terryberry et al. 1998; Poletaev et al. 2000; Zappia et al. 2002; Papachroni et al. 2007; Gruden et al. 2011; Yanamandra et al. 2011). Immunohistochemical staining of tissues from idiopathic and familial PD patients show dopaminergic neurons within the SN bind IgG, but not IgM, whereas tissues from age-matched controls and nonnigral control tissues show no detectable bound immunoglobulins (Orr et al. 2005). In one study, IgG reacted with 30% of the dopaminergic neurons within the nigra, and yielded positive correlations with numbers of MHC II^{+} and CD64^{+} (FcγRI) reactive microglia, yet yielded a negative correlation with disease duration. In PD patients, approximately 4% of the pigmented neurons contained Lewy bodies and all pigmented, Lewy body-containing neurons showed detectable IgG and α-syn within inclusions. This pattern of antibody reactivity was consistent with activated microglia and destruction of dopaminergic neurons in PD. Together these data suggest that endogenous antibodies of unknown specificity have the capacity to cross the BBB and bind cognate antigens expressed by dopaminergic neurons. Of interest, deletion of the FcγR by genetic ablation inhibits microglial activation and dopaminergic cell death in animal models of PD (He et al. 2002). Moreover, levels of antibodies to α-syn and catecholamine-derived melanin (neuromelanin) are increased in PD patients with antineuromelanin immunoglobulin binding shown to be more active in early disease (Double et al. 2009). Opsonization of cells or damaged neurons with antibody, targets the cells for phagocytosis and degradation by phagocytic macrophages, and also can activate the complement system, a major mediator of immune/inflammatory reactions. Interestingly, activation of the complement system may also be involved in neuronal death. Microglia are the only cells within the SN that express the initial recognition component of complement, C1q (Depboylu et al. 2011). Moreover, compared with controls, PD patients show increased areas of C1q-opsonized extracellular depositions of neuromelanin within the parenchyma, and C1q-expressing phagocytic microglia surround those areas, as well as cells around the luminal surfaces of the vasculature that express neuromelanin and C1q, suggesting a role for antiself antibodies and C1q-mediated clearing pathways in PD.

Along with activated microglia and astrocytes, T cells may also comprise components of PD pathobiology, although the mechanism(s) by which they effect disease remains enigmatic. Early autopsy evidence within the SN of PD patients showed increased numbers of CD8^{+} T cells in close proximity to activated microglia and degenerating neurons (McGeer et al. 1988a). More recently, both CD4^{+} and CD8^{+} T cells have been discovered within the SN of PD patients (Brochard et al. 2009). Although a dysfunctional BBB in PD patients may show some leakiness (Kortekaas et al. 2005), this may not be sufficient to allow unrestricted lymphocyte infiltration because CD4/CD8 ratios were 1:4.8 (Brochard et al. 2009) compared with the typical 2:1 ratio expected for peripheral T cells performing surveillance functions. Thus, the mechanism by which these T cells gain access to the SN, their activation state, and their function are questions that remain to be answered.

Peripheral immune aberrations, particularly in lymphocyte subsets, are abundant in PD patients. Total numbers of lymphocytes have been shown to be diminished by 17%, whereas CD19^{+} B cells are diminished as much as 35% and CD3^{+} T cells are diminished by 22% (Bas et al. 2001). Among CD3^{+} T cells, numbers of CD4^{+} T cells have been shown to be diminished by 31%, whereas numbers of CD8^{+} T cells are not significantly changed. A greater loss of naïve helper CD4^{+} T cells (CD45RA^{+}) and either unchanged or increased levels of effector/memory helper T-cell subset (CD29^{+} or CD45R0^{+}) have also been observed. Selective loss of CD4^{+}CD45RA^{+} cells are also detected in other neuropathological-associated disorders such as MS and Down's syndrome, suggesting a common immunological abnormality in neurological disorders (Fiszer et al. 1994a; Crucian et al. 1995). Increased frequencies of activated CD4^{+} T cells expressing Fas (Hisanaga et al. 2001) and increased IFN-γ-producing Th1 cells, decreased IL-4-producing

Th2 cells, and a decrease in $CD4^+CD25^+$ T cells have been found in the peripheral blood of PD patients (Baba et al. 2005), whereas circulating IL-15, RANTES, and IL-10 are significantly elevated in PD patients compared with controls (Rentzos et al. 2007, 2009). Evidence of increased mutual coexpression of CD4 and CD8 by $CD45R0^+$ T cells, increased expression of CD25 (α chain of the high-affinity IL-2 receptor) and TNF-α receptors, and diminished expression of IFN-γ receptors suggest that these T-cell subsets from PD patients are indeed activated. In addition to T cells that express α and β chains of the T-cell receptor ($TCR\alpha\beta^+$ T cells), elevated frequencies of T-cell populations expressing γ and δ chains of the T-cell receptor ($TCR\gamma\delta^+$ T cells) also have been found in the CSF of PD patients (Fiszer et al. 1994b) and are thought to play a regulatory role in CNS inflammation (Ponomarev and Dittel 2005; Bennett and Stuve 2009; Blink and Miller 2009). Moreover, a large proportion of the $TCR\gamma\delta^+$ T cells also express CD25, suggesting these CSF-obtained T cells are preferentially activated in PD patients (Fiszer et al. 1994b). One way in which the adaptive immune system could be mobilized to infiltrate the CNS during PD is through the drainage of aberrant forms of α-syn into the lymphatic system where the protein could activate lymphocytes. Indeed, in MPTP-intoxicated mice, α-syn drains to cervical lymph nodes where it activates antigen-presenting cells and T cells (Benner et al. 2008). An influx of α-syn-specific Th1 or Th17 effector T cells into the brain during PD could increase the inflammatory phenotype and neurotoxic response of microglia near dopaminergic neurons by increasing the concentration of proinflammatory molecules in the SN (Reynolds et al. 2010). Taken together, increased frequencies of memory and activated peripheral T-cell subsets, as well as those cells within the nigra of PD patients, suggest putative roles of T cells in disease progression, if not PD etiology. Although those roles have yet to be delineated, activated effector T cells (T_{eff}) or regulatory T cells (T_{reg}), the latter also showing an effector/memory T-cell phenotype, may migrate to the foci of inflammation in PD patients and either exacerbate or attenuate PD-associated neuroinflammatory responses and neurodegeneration. Thus, T_{reg} have the capacity to keep the disorder in check during the asymptomatic phase, whereas T_{eff} can accelerate disease progression (Fig. 1). Whether T-cell aberrations in PD patients reflect specifically activated effector or regulatory T-cell subsets and to what antigen(s) those T cells are induced, require answers to develop more precise immune-based therapeutic strategies.

ADAPTIVE IMMUNITY FOR THERAPEUTIC GAIN IN PD

It is likely that the adaptive immune system's response to disease in the CNS is similar in a range of neurodegenerative diseases. Thus, therapeutic strategies aimed at modulating the immune response during disease may be applicable to several neurodegenerative diseases. Here we will discuss recent approaches taken to modulate the adaptive immune system for disease therapy.

T_{reg} are an important subset of $CD4^+$ T cells that are known to maintain self-tolerance, prevent autoimmunity, and regulate immune homeostasis by attenuating excessive inflammation caused by pathogens or injury (Sakaguchi et al. 1995; Cederbom et al. 2000; Kipnis et al. 2002; Hori et al. 2003; Sakaguchi 2004; Coombes et al. 2005; Kim et al. 2007; Bourreau et al. 2009). They are identified by the expression of CD4 and CD25 cell-surface markers and by the transcription factor forkhead box P3 (FoxP3) in mice (Hall et al. 1990; Fontenot et al. 2003; Hori et al. 2003), and the expression of FOXP3, CD4, CD25, CD39, CD49d, and a lack of CD127 in humans (Fletcher et al. 2009; Kleinewietfeld et al. 2009). Although naturally occurring T_{reg} mature in the thymus, naïve $CD4^+$-stimulated T cells in the periphery can be polarized into an inducible T_{reg} (iT_{reg}) phenotype under certain conditions. For example, TGF-β, IL-2, IL-10, and all-trans retinoic acid are known to polarize T cells to iT_{reg} (Zheng et al. 2007, 2008; Khattar et al. 2009; Lee et al. 2009b), whereas histone deacetylase inhibitors are known to increase proliferation and suppressor activity of T_{reg} (Tao et al. 2007; Johnson

et al. 2008; Lucas et al. 2009; Saouaf et al. 2009). In vitro studies have shown that T_{reg} can suppress T_{eff} responses via cell-to-cell contact (Cederbom et al. 2000) and soluble factors (Wahl et al. 2004). T_{reg} can also inhibit the adaptive immune system indirectly by suppressing antigen presentation by APCs (Maloy et al. 2003). In the brain, T_{reg} promote neurotrophic support by inducing astrocytes to increase expression of brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) (Benner et al. 2004; Reynolds et al. 2007), and may promote glutamate clearance (Garg et al. 2008). Dysfunctional and reduced frequencies of T_{reg} are associated with several autoimmune diseases (Costantino et al. 2008), including multiple MS (Venken et al. 2008; Fletcher et al. 2009; Royal et al. 2009; Koen 2010), type 1 diabetes (Glisic et al. 2009), inflammatory skin disorders (Fujimura et al. 2008), autoimmune myasthenia gravis (Mu et al. 2009), and rheumatoid arthritis (Cao et al. 2003) as well as chronic inflammatory diseases such as systemic lupus erythematosus (Horwitz 2008; Venigalla et al. 2008; Barreto et al. 2009), asthma (Xue et al. 2007), inflammatory bowel disease (Bourreau et al. 2009), and immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, which is caused by a genetic mutation in the transcription factor FOXP3 (Bennett et al. 2001). Furthermore, T_{reg} are being investigated for therapeutic use in several of these diseases (Gonzalez-Rey et al. 2006; Brusko et al. 2008; Haas et al. 2009; Putnam et al. 2009; Vandenbark et al. 2009).

In our own works, T_{reg} can migrate from the periphery to the site of HIV-1-induced neuroinflammation in a mouse model of HIV-1 encephalitis (unpubl.). Adoptive transfer of activated $CD4^+CD25^+$ T_{reg} to HIV-1 encephalitic mice is neuroprotective (Liu et al. 2009). This study showed that adoptively transferred T_{reg} attenuated microgliosis and astrogliosis, increased expression of BDNF and GDNF expression, and down-regulated proinflammatory cytokines, oxidative stress, and viral replication, whereas effector $CD4^+$ T cells were not therapeutic (Liu et al. 2009). T_{reg} inhibit release of viral particles from HIV-1-infected human

mononuclear phagocytes (MP), kill infected cells, and induce phenotypic changes in MP (Huang et al. 2010). Up-regulation of the antiviral ubiquitin-like protein, interferon-stimulated gene 15 (ISG15) was concordant with the decrease in viral release from MP, and implicating caspase-3 and granzyme/perforin pathways in MP killing. Finally, it was shown that T_{reg} induce the phenotypic switch of MP from the neurotoxic MI phenotype to the more neurotrophic M2 phenotype with the down-regulation of iNOS and up-regulation of arginase 1. In the MPTP mouse model, T_{reg} control microglia function by suppressing reactive oxygen species production and NFκB activation via mechanisms that modulate redox enzymes, cell migration, and phagocytosis (Reynolds et al. 2007, 2009, 2010). Furthermore, the adoptive transfer of T_{reg} leads to >90% protection of dopaminergic neurons within the nigrostriatal system, whereas adoptive transfer of Th1 or Th17 T_{eff} exacerbate neuronal degeneration and cotransfer of T_{reg} with Th1 or Th17 increases the protective effect (Reynolds et al. 2010). Together, these data suggest that T_{reg} may be used to suppress the activity of the innate and adaptive immune responses operative in HIV-1 neurodegeneration and PD pathogenesis by transforming the neurotoxic phenotype of activated microglia, Th1, and Th17 cells.

PROSPECTS TOWARD EFFECTIVE IMMUNOTHERAPEUTICS FOR PD

Over the past decade, immunization strategies have been proposed to combat disease progression for neurodegenerative disorders, but principally for AD. Such strategies readily induce humoral immune responses against misfolded protein aggregates to facilitate their clearance in diseased brain tissue. However, such activities also induce robust adaptive immunity against the same misfolded proteins and serve to accelerate disease progression. This is precipitated by induced effector T-cell responses that can lead to encephalitis and profound neural injuries, and has led investigators to search for mechanisms that attenuate such adaptive neurotoxic immune responses. We posit that the
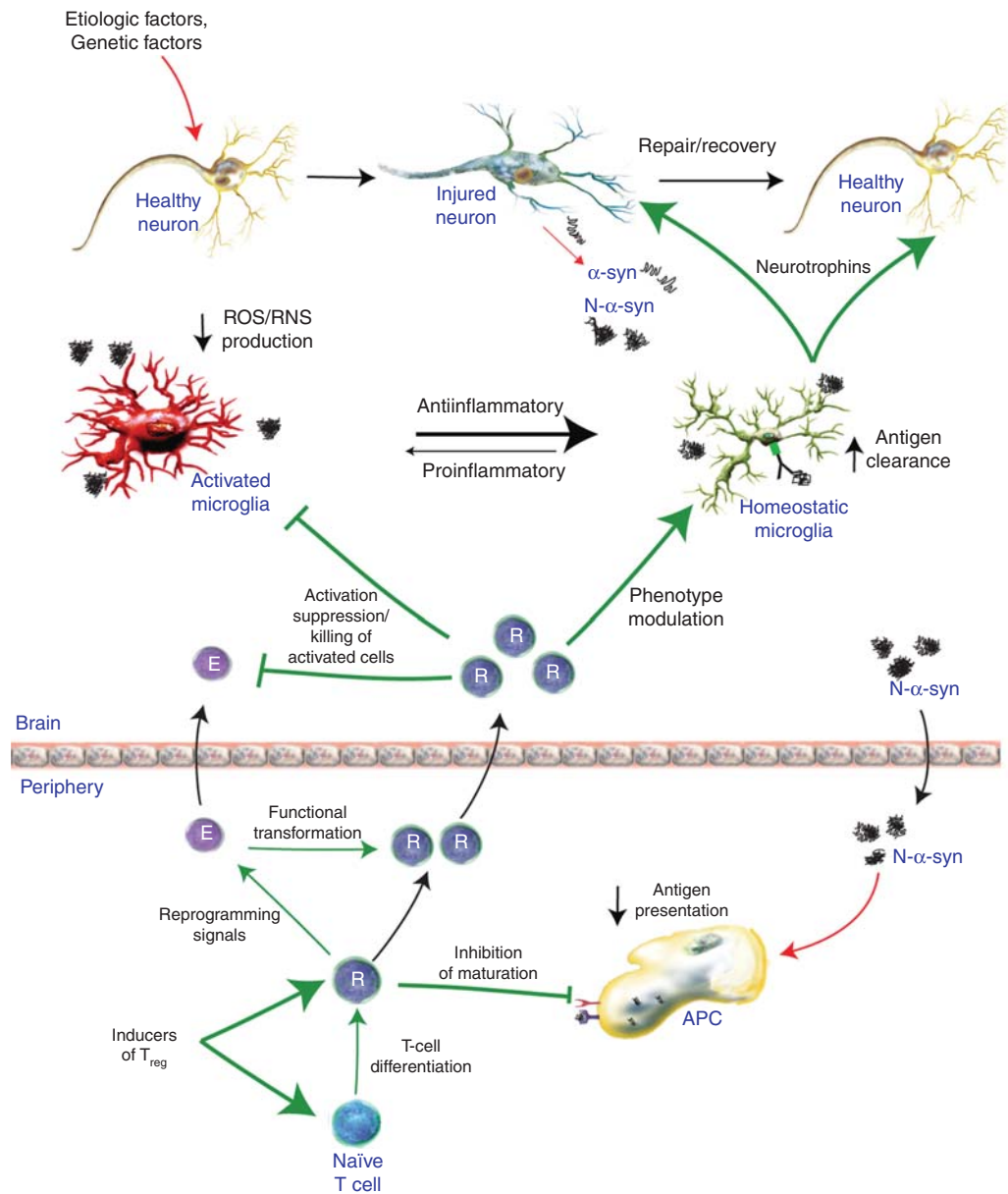
Figure 2. Adaptive immunity for therapeutic gain. Regulatory T cells (T_{reg}, R) work to control excessive inflammation and may be harnessed to control neuroinflammation in PD and other neurodegenerative diseases. T_{reg} can modulate microglia and other immune cells away from proinflammatory responses to anti-inflammatory/homeostatic functions. Therefore, strategies aimed at inducing, boosting, or reprogramming T_{reg} responses (e.g., functional transformation of T_{eff} [E] to T_{reg}, increasing nT_{reg} numbers, or activating T_{reg} in an antigen-specific manner) show promise as possible disease-modifying therapies. T_{reg} can modulate immune responses via several mechanisms, including suppressing microglia activation, inducing microglia phenotypic switching (toward anti-inflammatory), killing activated cells (e.g., T_{eff} and microglia), and inhibition of APC maturation and antigen presentation. All together, T_{reg} may suppress innate and adaptive proinflammatory, neurotoxic immune responses and boost homeostatic, neurotrophic immune responses resulting in slowing of neurodegeneration and allowing repair of damaged neurons. Such strategies may help to slow or halt the progression of PD.

T_{reg} responses in PD are dysfunctional during advanced disease states. As such, this serves to shift the balance from regulatory to effector T-cell activities, and yields an inability to attenuate ongoing neurotoxic inflammatory events (Fig. 2). If clearance of misfolded proteins can be achieved with subsequent immune modulation and restoration of T_{reg} responses, improved therapeutic outcomes for neuronal protection would be realized. This may be achieved through advances in immune regulation used to achieve a homeostatic glial response for therapeutic gain.

SUMMARY AND CONCLUSIONS

No doubt, the role of inflammation in PD is now well appreciated. This is supported by data seen in a growing number of laboratory and animal investigations as well as in human studies. Inflammation is linked to the extracellular appearance of brain protein modifications and aberrant protein misfolding, which remain prominent hallmarks of PD-associated dopaminergic neurodegeneration. During disease, dopaminergic neurons accumulate α-synuclein together with other misfolded proteins seen as intracellular Lewy body inclusions. On injury or death, neurons release these proteins to the surrounding neuroenvironment and the modified proteins find their way to the peripheral lymphatic system. In an attempt to clear and digest cellular debris, microglia and blood-borne macrophages infiltrate sites of neuronal injury and death and convert to a proinflammatory activated state. Misfolded and modified α-synuclein species draining from these sites also have the capability to activate antigen-presenting cells in peripheral lymphoid tissues inducing effector neurotoxic T-cell responses. This normally serves to facilitate debris clearance and repair functions. Indeed, under steady-state conditions and early in disease, activated microglia and adaptive immune responses are limited. Nonetheless, as disease becomes more robust, activated microglia are seen in abundant numbers removed from proximate areas of neuronal death. This may be attributable to the failure of activated microglia to return to a homeostatic state. Thus, disease-affected microglia are in a constant activation flux, oscillating between homeostatic and activation states. Interestingly, whereas this cell maintains an activated amoeboid phenotype, microglial functional profiles can encompass a broad range of responses that range from an M1 (proinflammatory neurotoxic) to M2 (anti-inflammatory neuroprotective) activities. Such evolution in cell function may be driven by the deposition and release of nondegradable modified proteins or by infiltrating T lymphocytes. Once modified protein species enters the peripheral lymphoid tissues, activate antigen-presenting cells, and are presented as neoepitopes, adaptive immune responses are induced. Subsequent induction of effector T-cell-mediated responses may profoundly affect microglial states or directly kill neurons. As disease evolves, these responses emerge from a well-regulated neuroprotective state to loss of regulatory function and disease. In this scenario, the engagement of therapeutic strategies that dampen inflammatory and neurotoxic profiles by induction or repair of aberrant regulatory T-cell responses could provide a means to reverse the neurodegenerative process. Thus, modulation of inflammatory responses for therapeutic gain remains an ever-pressing directive to improve disease outcomes.

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