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CD4+ T cells for the pathobiology of neurodegenerative disorders

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Abstract

CD4+ T cells orchestrate innate and adaptive immunity. In the central nervous system they modulate immune responses including cell trafficking and glial neuroregulatory functions through an array of soluble molecules cell-cell interactions affecting tissue homeostasis. During disease their roles evolve to an auto-aggressive or, alternatively, protective phenotype. How such a balance is struck in the setting of neurodegenerative disorders may reflect a dichotomy between regulatory T cell, anti-inflammatory and neuroprotective activities versus effector T cell inflammation and neurodegeneration. Interestingly, such roles may show commonalities amongst neurodegenerative diseases. Herein we focus on strategies to modulate such CD4+ T cell responses for therapeutic gain.

Keywords

MGC, Microglia; PD, Parkinson's disease; AD, Alzheimer's disease; HAND, HIV-1 associated neurocognitive disorders; MP, mononuclear phagocytes; Treg, regulatory T cells; Teff, effector T cells

1. Introduction

CD4+ helper T lymphocytes (Th), CD4+ regulatory T lymphocytes (Treg) and CD8+ cytotoxic T lymphocytes (CTL) are subset classifications that have undergone significant phenotypic and functional changes in recent years (Germain, 2002; Shevach, 2002). In regards to the former and despite its profound functional roles in immunoregulation, CD4+ T cells, have no purported phagocytic activity and do not kill pathogens directly, but serve to activate and direct the functions of other cells to do its bidding (Zhu and Paul, 2008). These activities include antibody class switching for B cells, CTL activation and mobilization, as well as mononuclear phagocytes (MP; blood borne monocytes, tissue macrophages and microglia) phagocytic and intracellular killing activities (Hume et al., 2002; Parker, 1993; Van Ginderachter et al., 2006; Yamamoto et al., 2008; Zhu and Paul, 2008). As described, CD4+ T cells possess limited mechanisms for cell killing such as granulysin and Fas-mediated apoptosis. Such immune

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functions are central tenets held for conventional immunology (Bevan, 2004; Castellino and Germain, 2006; Zhu and Paul, 2008). Starting in the mid to later 1980s, CD4+ helper T cells were divided into Th1 and Th2 subsets based on their cytokine profiles and effector functions (Mosmann et al., 1986; Mosmann and Coffman, 1989). Now, more than twenty years later, the phenotype and function of T cell subsets have evolved once again with the description of regulatory (Tr1, Th3, Treg) and Th17 cell phenotypes (Fontenot et al., 2003; Hori et al., 2003; Sakaguchi et al., 1995; Weaver et al., 2006). Moreover, CD4+ T cell function in health and disease has evolved significantly following the discovery of its central role as a cellular target for human immunodeficiency virus (HIV) infections (De Boer, 2007; Grossman et al., 2002; Ho et al., 1995).

In regards to the brain, the role played by CD4+ T cells have only recently been appreciated beginning less than two decades ago (Hickey et al., 1991). Indeed, the brain was previously regarded as an immune privileged organ, but only recently has it been shown that such privilege is limited (Bechmann et al., 2007; Chen and Palmer, 2008). The idea of such 'immune privilege' was based previously on its limited abilities to withstand damage during inflammation and its relatively poor regenerative capacity. However, both innate and adaptive immunity are vibrant despite any limitations conferred by the blood-brain barrier (Bechmann et al., 2007; Chen and Palmer, 2008). The known active role of both afferent and efferent arms of adaptive immunity results in antigen drainage to the cervical lymph nodes and active immune responses that affect neurodegenerative activities during disease and is now well appreciated (Galea et al., 2007; Kierdorf et al., 2009; Perry et al., 2007; Theodore et al., 2008). There are several reasons for this. *First*, in an activated state, CD4+ T cells can readily cross the blood-brain-barrier (BBB) (Engelhardt and Ransohoff, 2005; Gonzalez-Scarano and Martin-Garcia, 2005). *Second*, in regards to function, recruitment of peripheral leukocytes into the central nervous system (CNS) during neuroinflammatory, infectious and neurodegenerative diseases (for example, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and HIV-1 associated neurocognitive disorders (HAND, and stroke) serves both in protective and disease-accelerating processes (Appel, 2009; Banerjee et al., 2008; Benner et al., 2008; Brochard et al., 2009; Carrithers et al., 2000; Liu et al., 2009; Planas and Chamorro, 2009; Theodore et al., 2008). *Third*, although much is known in regards to the role played by CD4+ T cells as immune modulators and surveillance of microbial pathogens and neoplasia, it is only within the past five years that a dialogue between peripheral immunity and degenerative diseases of the CNS has been appreciated (Appel, 2009; Benner et al., 2008; Benner et al., 2004; Brochard et al., 2009; Byram et al., 2004; Clausen et al., 2007; Garg et al., 2008). Thus, this review focuses on the latter and serves to outline and describe a newly advancing field of adaptive immunity for neurodegenerative diseases. Particularly, we will outline how and under what conditions CD4+ T cells could elicit neuroprotection or neurotoxicity and how might these responses be utilized for diagnostic and therapeutic gain.

2. Neurodegenerative disorders and immunity

Neurodegenerative disorders are defined neuropathologically within specific brain regions by significant neuronal loss accompanied by neuroinflammatory astroglio- and microgliosis (Selkoe, 1994). Commonly, dysfunction of selected brain circuits initiates synaptic damage prior to neuronal loss. Indeed, decreased neuronal numbers follows neuronal dysfunction (Mosley et al., 2006). The clinical manifestations of disease that include impairments of memory, behavior, personality, judgment, attention, language (amongst other executive functions) as well as movement and gait characteristic of AD, PD, ALS, and HAND (Appel, 2009; Appel et al., 2008; Beers et al., 2008; Gonzalez-Scarano and Martin-Garcia, 2005; Vesce et al., 2007). Although the causes of each are divergent, cell-mediated processes in disease pathogenesis are similar. Moreover, the brain is limited in the ability to respond to injuries including regulation of inflammation, first and foremost (Appel, 2009; Peterson and Fujinami,

2007; Tansey et al., 2007). In recent years, relationships between neuroinflammation, adaptive immunity, and neurodegenerative have been sought (Appel, 2009; Mosley et al., 2006; Tansey et al., 2007). Nonetheless, the major focus of research and therapeutic development remain on innate immunity and the primary roles of astrocytes and microglia in disease (Farina et al., 2007; Hanisch and Kettenmann, 2007). Indeed, relationships between adaptive immunity and neurodegeneration or neuroprotection were until very recently, less well pursued. Thus, the role of effector and regulatory CD4+ T cells should be and is herein a primary focus. We begin with a brief review of common neurodegenerative disorders and previous knowledge regarding the role the immune system plays in neurodegenerative disease.

AD is the first most common neurodegenerative disease and the leading cause of senile dementia worldwide (Kawas and Brookmeyer, 2001). It is a progressive dementia first described by German psychiatrist Alois Alzheimer in 1906 (Graeber et al., 1997). Clinically, AD symptoms of cognitive and behavioral deficits are concordant with neuronal loss and atrophy in brain regions linked to learning and memory (Caselli et al., 2006; Goedert and Spillantini, 2006; Graeber et al., 1997). Such impairment ultimately results in severe disability for social and occupational functions (Harrington et al., 2007; Markesbery and Lovell, 1998; Tabert et al., 2005). The multifaceted causes of AD include genetic, environmental, and dietary factors but the precise etiology awaits discovery (Goedert and Spillantini, 2006; Graeber et al., 1997). Currently, there are three competing hypotheses for disease neuroopathogenesis. The first is cholinergic, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine (Francis et al., 1999); the second is amyloidogenic, which postulates that accumulation of amyloid beta (Aβ) deposits resulting from protein aggregation and/or over-expression are the fundamental cause of neuronal impairments (Bishop and Robinson, 2002; Hardy and Selkoe, 2002; Lee et al., 2006); the third is tauogenic, which suggests that the tau protein abnormalities initiate the cascade of neurofibrillary tangles and plaques with concomitant alterations in dendritic arbor and neural physiology (Mudher and Lovestone, 2002). Based on these, two distinct, but not mutually exclusive theories on AD, other neuropathogenesis theories were introduced and included the “positive feed-forward” and “insult” theories. The former proposes that aberrant Aβ activates MPs, stimulating the release of various inflammatory cytokines, chemokines and excitotoxic factors that stimulate neurons to produce more Aβ. The latter theory suggests that some “insults”, including genetic predisposition, cause an initial neuronal damage with deposition of debris that could not be digested inefficiently by microglia, which result in microglia over-activation and chronic inflammation. In addition, complement deposition and lymphocyte infiltration might amplify the inflammatory response and cause more neuronal death (Goldgaber et al., 1989; Kadiu et al., 2005; McGeer and McGeer, 1995; Schmechel et al., 1988). Both theories highlight the importance of neuroinflammation (Hanisch and Kettenmann, 2007; McGeer and McGeer, 1995; Rogers et al., 2007; Walker and Lue, 2005) and genetic factors including mutation of presenilin-1 (PS-1) (Chen et al., 2008b; Das, 2008; Wang et al., 2007; Yukioka et al., 2008), presenilin-2 (PS-2) (Lleo et al., 2001; Schellenberg, 2003; Steiner et al., 1999; Wolozin et al., 1996), and apolipoprotein E (ApoE) polymorphisms (Pericak-Vance et al., 1991). Neuroinflammation is initiated by resident glial cells (microglia, astrocyte and perivascular macrophage) and potentially amplified by infiltration of peripheral immunocytes (T lymphocyte, B lymphocyte and dendritic cells) (Benner et al., 2008; Blasko and Grubeck-Loebenstein, 2003). The interplay between immunity, genetics, and environment do affect AD pathobiology; however, the relative influences of each over the other are not yet well appreciated.

PD is second to AD in disease prevalence (Nussbaum and Ellis, 2003). Like AD, PD is progressive and does show, in some forms, clear genetic linkages (Tansey et al., 2007). In 1817, the clinical features of PD were first described by James Parkinson in his classic monograph “An Essay on the Shaking Palsy” (Lees, 2007; Parkinson, 2002). However, after

almost two centuries, the available therapeutic strategies remain symptomatic due, amongst other factors, to a limited understanding of the molecular neurobiology and pathobiology of the disease. In regards to the neuropathology, dopaminergic neurons in the substantia nigra pars compacta (SNpc) are lost along with their connections to the striatum (comprised by the caudate nucleus and putamen) and the presence of intraneuronal proteinacious cytoplasmic inclusions termed “Lewy bodies” (Barzilai and Melamed, 2003; Dauer and Przedborski, 2003; Fiskum et al., 2003; Michel et al., 2002; Paleologou et al., 2009). Recently, studies of PD pathogenesis have led to the prevailing hypothesis that misfolded proteins and dysfunction of the ubiquitin-proteasome pathway is pivotal to PD pathogenesis (Bennett et al., 1999; Dauer and Przedborski, 2003; Fishman and Oyler, 2002; Hattori et al., 2003; Hattori et al., 2000; Tanaka et al., 2004). In addition, mitochondrial dysfunction and oxidative stress is linked to PD development (Mosley et al., 2006; Tansey et al., 2007), which also have been shown to contribute dopaminergic neuronal loss (Albers and Beal, 2000; Benner et al., 2004; Ogawa et al., 2004; Reynolds et al., 2007a; Zhu et al., 2004). Like in AD, neuroinflammation is a strict feature associated with disease pathogenesis and progression (Bartels and Leenders, 2007; Benner et al., 2008; Mosley et al., 2006; Rogers et al., 2007; Tansey et al., 2008; Tansey et al., 2007; Wahner et al., 2007; Whitton, 2007). Neuroinflammation can accelerate dopaminergic neuronal death (necrosis and/or apoptosis), which can itself amplify neuroinflammation in a paracrine manner (Tansey et al., 2007).

Genetic factors and environmental cues are thought to play roles in familial and sporadic PD. The latter is dominant in post-encephalitic and chemical-induced PD, such as rotenone and 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP). Currently, six genes have been identified to be associated with high penetrant autosomal dominant or recessive PD, including mutations in the gene encoding α-synuclein, parkin, DJ-1, ubiquitin c-terminal hydrolase-1, PTEN-induced kinase 1, and leucine rich repeat kinase 2 (Lee and Liu, 2008; Shimura et al., 2000; Volles and Lansbury, 2002; Volles et al., 2001). Such mutations have provided insight into the pathogenesis of PD. For example loss of function of parkin results in dysfunction of the ubiquitin-proteasome system; whereas, mutations in PTEN-induced kinase 1 and DJ-1 result in mitochondrial dysfuction and oxidative stress (Rogaeva et al., 2004; Takahashi-Niki et al., 2004). These observations support common pathogenic mechanisms associated with protein aggregation, mitochondrial dysfunction, and oxidative stress in AD and PD, linked in severity to neuroinflammatory responses (Rogers et al., 2007).

The neuropathology of ALS, also known as Lou Gehrig’s disease, is characterized by weakness and atrophy of muscles, which are denervated from both upper and lower motor neurons in the brainstem and spinal cord (Charles and Swash, 2001; Martin et al., 2000; Pradat and Bruneteau, 2006). Studies using transgenic mouse models and patient tissue delineated that the causes of ALS appear to be multifactorial, including environmental and genetic factors (Shaw and Wilson, 2003). The former implicates factors associated with viral infection, heavy metals, trauma, and experimental neurotoxins, while the latter suggests that mutations in the genes encoding Cu/Zn superoxide dismutase (SOD1), neurofilament H gene, the astrocytic-specific glutamate transporter, excitatory amino acid transporter (EAAT2, GLT1), and most recently, fused in sarcoma (FUS) (Bruijn et al., 2004; Cluskey and Ramsden, 2001; Kwiatkowski et al., 2009; Lee et al., 2002; Tu et al., 1997; Vance et al., 2009). Other risk factors, such as oxidative stress, glutaminergic excitotoxicity, abnormal enzyme metabolites, aberrant protein aggregation, and peripheral immune abnormalities may directly participate in the pathogenesis of ALS (Appel, 2009; Banerjee et al., 2008; Bruijn et al., 2004). Finally, evidence of neuroinflammation in ALS patients and experimental models demonstrates a pivotal role in disease and its progression (McGeer and McGeer, 2002).

HAND commonly follows progressive HIV-1 infection. A central feature of HAND is “severe neuronal dysfunction without loss”, which ranges in clinical severity from subtle deficits to

incapacitating dementia: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD) (Ellis et al., 2007; Gonzalez-Scarano and Martin-Garcia, 2005). Early in the AIDS epidemic, about 20–30% of individuals infected with HIV-1 developed a range of cognitive and motor symptoms, including impaired short-term memory, reduced concentration and muscle weakness (Gendelman et al., 1997; Gonzalez-Scarano and Martin-Garcia, 2005; Williams et al., 2001). These symptoms often occur concomitant with behavioral symptoms, such as personality changes, apathy and social withdrawal, and even led to a near vegetative state referred to as HAD. However, the advent and widespread use of combinatorial antiretroviral therapy (ART) markedly reduced the incidence of overt disease. Simultaneously, the prevalence of ANI and MND continue to increase, which suggests that onset and progression of HAND is linked, in part, to viral load and diminished adaptive immunity (Ellis et al., 2007; Gendelman et al., 1997; Gendelman et al., 1998; Gonzalez-Scarano and Martin-Garcia, 2005; Peterson and Fox, 2001; Reynolds et al., 2007a; Reynolds, 2007). Clinical manifestation of HAND evolves into the triad of cognitive, behavior and motor dysfunction induced by axonal disruption and “pruning” or aberrant sprouting of synaptodendritic connections (Ellis et al., 2007; Ghorpade et al., 1998; Gonzalez-Scarano and Martin-Garcia, 2005; Zheng and Gendelman, 1997).

HIV-1 enters the brain and is found in cerebrospinal fluid after primary infection, however, the mechanism by which HIV-1 invades the CNS is still limited. The CNS is separated by the BBB and the cerebrospinal fluid is separated by choroid-plexus epithelium. Both barriers are selectively permeable to regulate the traffic of cells and substances from bloodstream into the CNS. Even the “invasion” of peripheral immune cells across the BBB as normal immune surveillance is carefully regulated. Entry of HIV-1 to the CNS has been studied using animal models and cell culture systems for more than 20 years. Several hypotheses of CNS infection have been postulated from those studies. The “Trojan horse” hypothesis proposes that HIV-1 passes the BBB as sequestered passengers in infected cells that are trafficking to the brain (Meltzer et al., 1990). Other studies have suggested that HIV-1 might enter the CNS as free virus, as well as through transcytosis of endothelial cells (Buescher, 2007; Ellis et al., 2007; Gendelman et al., 1997; Gonzalez-Scarano and Martin-Garcia, 2005). After entry into the brain, HIV-1 disrupts disrupts neuronal function either directly through interaction with HIV-derived proteins/nucleic acid (direct effect) (Brenneman et al., 1994; D’Aversa et al., 2005; Eugenin et al., 2005; Spector and Zhou, 2008) or indirectly by HIV-induced cytokines and chemokines form MPs (Buckner et al., 2006; Chadwick et al., 2008; Mollace et al., 2001; Roberts et al., 2003; Wesselingh and Thompson, 2001; Yeh et al., 2000). Which factors are most deleterious and the extent by that each affects neuronal function remain central questions for the pathobiology of neurodegenerative disease.

3. Neural stem cells and innate immunity

Neurons, astrocytes, oligodendrocytes and microglia are the principal cell populations in the brain. Recent studies on neuronal plasticity have challenged paradigms established by Santiago Ramón y Cajal and others (Lopez-Munoz et al., 2006). One study indicated that microglia progenitors can transdifferentiate into neurons, astrocytes and oligodendrocytes, suggesting a novel role of microglia as multipotential stem cells (Yokoyama et al., 2004); whereas, astrocyte and oligodendrocyte progenitors can transdifferentiate into neurons (Doetsch et al., 2002), suggesting a novel role for these cell populations as multipotential stem cells. Neurogenesis requires two important growth factors, epidermal growth factor (EGF) (Doetsch et al., 2002) and fibroblast growth factor (FGF). Recently, evidence demonstrates roles for vascular endothelial growth factor (VEGF) in neurogenesis and neurovascular signaling deficits in neurodegeneration (Zacchigna et al., 2008).

Innate immunity is the first defense against pathogenic insults (Takeuchi and Akira, 2007). Several advantages of the innate immune system over the adaptive immune system include mechanisms that are germline-encoded, constitutively present, and immediately reactive, as well as mechanisms that have broad molecular-pattern recognition, non-specific effector function, and do not require immune memory formation (Akira et al., 2006; Farina et al., 2007). Innate molecules, such as pattern recognition receptors (PRRs) and the complement system are also included (Akira et al., 2006; Klotman and Chang, 2006; Rivest, 2003). In other words, the innate immune system is hard-wired for immediate and broad reactivity against foreign insult. The innate immune system consists of mast cells, neutrophils, natural killer cells (NK), gamma-delta T cells, natural killer T cells (NKT) and mononuclear phagocytes (MPs; monocyte, macrophages and dendritic cells) (Calandra and Roger, 2003; Ghorpade, 2008; Hammad and Lambrecht, 2008; Hume et al., 2002; Sternberg, 2006; Yamamoto et al., 2008). In the following part of this review, we will emphasize the function of MPs and their PRRs in health and disease (Kadiu et al., 2005; Okun et al., 2008; Seitz, 2003).

The function of innate immunity is to coordinate among all innate cells and molecules the proper cooperation for systemic scanning necessary for immune surveillance and homeostasis maintenance (Hanisch and Kettenmann, 2007; Mosser and Edwards, 2008). After being activated by injury, tumor or pathogen, the innate immune system functions focus on clearance of pathogens and debris, tissue repair, and in orchestrating adaptive immune responses (Hanisch and Kettenmann, 2007; Mosser and Edwards, 2008; Pichlmair and Reis e Sousa, 2007). Within the CNS main executors of innate immunity are perivascular macrophages and microglia (Kadiu et al., 2005). The primary function of ‘resting’ microglia is to engulf cellular debris and metabolic waste; whereas, the adjunct role of ‘resting’ microglia is to synthesize and secret neurotrophins; usually attributed to the primary role of astrocytes (Hanisch and Kettenmann, 2007; Streit, 2006). In response to pathological conditions, microglia transform into reactive state (Glanzer et al., 2007; Hanisch and Kettenmann, 2007) and the role of microglia switches from a phagocytic and neurotrophic phenotype to a reactive phenotype expressing toxic and reparative functions (Streit, 2006). The intent of inflammation is to eliminate pathogen and repair injury (Schwartz et al., 2006; Streit, 2006). However, the consequences of uncontrolled inflammation cause energy exhaustion and injury exacerbation have been reported (Tansey et al., 2008; Tansey et al., 2007). To date, the role of neuroinflammation for CNS disease is still argued.

Astrocytes are the most abundant cells in the CNS and together with microglia actively participate in local innate immunity triggered by injury and disease (Farina et al., 2007). Usually, in contrary to microglia, the job of the astrocyte is to support neuronal structure and function by neurotrophin production, ion maintenance and neurotransmitter modulation (Dong and Benveniste, 2001; Farina et al., 2007). In addition, astrocytes possess a series of receptors involved in innate immunity such as toll-like receptors and scavenger receptors, and soluble mediators including cytokines and chemokines (Dong and Benveniste, 2001; Farina et al., 2007). Using those sensors, astrocytes sense injurious insults. Therefore, following CNS insult, astrocytes work together with microglia to remove pathogens and restore homeostasis, actively and passively (Falsig et al., 2006; Farina et al., 2007). Astrocytes also promote leukocyte recruitment and amplify CNS inflammatory responses (Farina et al., 2007). The appearance of astrogliosis and microgliosis in specific brain regions where neurodegenerative scars form are thought to be primary or secondary culprits of neurodegeneration, regardless of their contribution to protective acute neuroinflammation as a primary function (Tansey et al., 2007). To some extent, such prejudiced idea was born out of misconceptions about the nature and function of reactive gliosis was rooted in cell-culture studies, in which endotoxin-treated microglia produce potential secretory neurotoxins. These include, but are not limited to, proinflammatory cytokines, quinolinic acid, arachidonic acid and its metabolites, and reactive oxygenic species (ROS). These have branded microglia as inducers of neurodegeneration

rather than simple sensory and versatile effector cells (Schwartz et al., 2006; Streit, 2006). A neurodegenerative microglial reaction may occur as a consequence of the microglia's primary role to eliminate misfolded protein or to attempt repair infectious injury as in HAND or an attempt to heal injury. What appears to worsen disease, however, is neurodestructive chronic neuroinflammation. A singular strategy in designing protective immune therapies rests in coping with the aberrantly altered homeostatic environment as the immune responses, under disease conditions, become both ineffective and disease progressive. These processes thus warrant therapeutic intervention with anti-inflammatory drugs or through induction of regulatory adaptive immune responses (Tansey et al., 2007).

As the most important molecules in innate immunity, pattern recognition receptors (PRRs) are constitutively expressed in the host and are highly conserved among species. Members of PRR families, such as toll-like receptors (TLRs) and NOD-like receptors (NLRs), recognize the evolutionarily conserved motifs of pathogen-associated molecular patterns (PAMPs), which include bacterial carbohydrates, nucleic acids, lipotechoic acids and fungal glycans (Akira et al., 2001; Farina et al., 2007; Imler and Hoffmann, 2001; Medzhitov, 2001). TLRs are expressed by both immune and non-immune cells (Farina et al., 2007; Hou et al., 2008; Medzhitov, 2001). Within the CNS, microglia, astrocytes, oligodendrocytes and neurons express different TLR profiles (Hanisch et al., 2008). Those TLRs function cooperatively to trigger and tailor innate immune response, as well as adaptive immune response at various points during a response (Akira et al., 2001; Pasare and Medzhitov, 2004). As sensors of danger signals, the nature of TLRs is supposed to be neuroprotective in an evolutionary context (Hanisch et al., 2008; Pasare and Medzhitov, 2004). For example, TLRs are regarded as means to prevent pathogen infection and promote plaque clearance (Hanisch et al., 2008). The observations that activation of immune cells through TLR ligation can induce the production of copious amounts of proinflammatory cytokines, especially when over-stimulated, promoted the notion of a more neurotoxic phenotype (Farina et al., 2007; Okun et al., 2008). Those cytokines, though essential for pathogen elimination and immune modulation, are detrimental for neuronal vitality when bystander damage outweighs the benefits of clearance mechanisms (Farina et al., 2007; Okun et al., 2008).

4. Adaptive immunity

Adaptive immunity, which is also called acquired immunity, is involved in later phases of infection. In contrast to innate immunity, several features particular to adaptive immunity which include mechanisms of somatic-rearrangement, induciblity, delayed reactivity, atomic-pattern recognition, high specificity, and memory (Vivier and Malissen, 2005). The adaptive immune system consists of two main cell populations, T lymphocytes and B lymphocytes, and two huge molecular repertoires, T cell receptors (TCRs) and B cell receptors (BCRs) provided by a capacity for somatic recombination of their antigen receptor genes (Vivier and Malissen, 2005). The generation of diversity among TCRs and BCRs is provided from segment rearrangement for combinatorial diversity and nucleotide recombination for junctional diversity (Nadel and Feeney, 1995). With diversity plus degeneracy, the adaptive immune system has the capacity to generate receptors capable of recognizing highly specific epitopes (Margulies, 2003; Martinez-Hackert et al., 2006; Reiser et al., 2003).

4.1. Adaptive immunity, homeostasis and surveillance

There are two forms of adaptive immunity. Humoral immunity is mediated by antibodies secreted by B lymphocytes, while cell-mediated immunity is executed by T lymphocytes (Vivier and Malissen, 2005). In health, both humoral immunity and cell-mediated immunity play important roles in immune surveillance and homeostasis maintenance (Vivier and Malissen, 2005). In disease, they work cooperatively to clear pathogens and form immunological memory (Vivier and Malissen, 2005). Neutralizing effects and opsonizing

effects are typical effector mechanisms of antibodies secreted by B cells, while helper and cytotoxicity are typical effector mechanisms of T cells. The two types work collaboratively to exert adaptive immunity (Vivier and Malissen, 2005). Normally, the brain was considered as "immune-privileged" organ whereby T and B cells were thought to be excluded. However, as "immune-privileged" in the brain is not absolute, this notion has been rejected (Chen and Palmer, 2008). Both T cells and B cells are found to be present in both healthy and diseased brain (Chen and Palmer, 2008).

4.2. B cells

B cells carry out humoral immunity. Albeit seldom reported to be present in the brain during homeostatic conditions, during disease evidence of humoral immune responses in the initiation and modulation of neurodegeneration came from findings of experimental models wherein dopaminergic neurodegeneration was triggered by passive transfer of immunoglobulin from PD patients to mice (He et al., 2002). It was estimated that this effect was mediated by interaction of IgG and FcgammaR1, which are expressed by activated B cells and microglia, respectively.

4.3. T cells

T cells play a central role in adaptive immunity, not only in cell-mediated immunity, but also in humoral immunity (Vivier and Malissen, 2005). They are widely distributed in all tissues. Typically, T cells circulate in the body fluid until recognition by their TCR of its cognate antigen presented in the context of the MHC molecules by antigen presenting cells (APCs) located within secondary lymphoid organs. After activation, T cells undergo massive proliferation and expansion, and elicit effector functions either by cell-cell contact or cytokine release, including mediating activation of B cells, modulation of innate immune cell function, or inducing target cell death (Vivier and Malissen, 2005). According to different phenotypes and functions, T cells are divided into two populations, Th and CTL (Vivier and Malissen, 2005). Moreover, CD4+ T cells can be subdivided into conventional T cells (effector T cells and memory T cells) and regulatory T cells (Tregs, including natural occurring Tregs and adaptively induced Tregs) (Grossman et al., 2004a). Because HIV-1 infects these cells, intense study on CD4+ T cell behavior and function has evolved (De Boer, 2007; Grossman et al., 2002; Ho et al., 1995).

Few T lymphocytes patrol for immune surveillance of the normal brain (Chen and Palmer, 2008). Under injurious or disease conditions, more T lymphocytes, but not B lymphocytes, infiltrate into the site of brain injury (Appel, 2008; Brochard et al., 2009; Engelhardt and Ransohoff, 2005). Leukocyte recruitment is cell- and site-specific, thus infiltration is not likely due to massive disruption of the BBB (Appel, 2008; Brochard et al., 2009; Engelhardt and Ransohoff, 2005). Under neurodegenerative conditions, a high ratio of activated T lymphocytes is found circulating within the peripheral blood, thus raising the question as to whether those activated T lymphocytes came from the brain, or are they destined to infiltrate the brain. Currently, no related study has been posed to address those possibilities. Additionally, the presence of activated peripheral T cells, suggests a role in neurodegeneration. As for the contribution of infiltrating T lymphocytes to neurodegeneration, different groups have opposite opinions. Brochard et al reported that the presence of CD4+ T cells in postmortem substantia nigra of PD patients as well as in the MPTP-induced PD model, is neurodestructive (Brochard et al., 2009). Previous reports however show that while infiltration of effector CD4+ T cells is neurodestructive, infiltration of CD4+ Treg is neuroprotective (Reynolds et al., 2007b). Moreover, extravasation of CD4+ T cells in the mutant SOD1 transgenic ALS mouse model is neuroprotective (Beers et al., 2008).

5. Effector T cells and neurodegenerative diseases

After activation, naïve CD4+ T cells (Th0) begin clonal expansion. Depending on different stimuli and APC signals, they differentiate into different subtypes and are classified by different cytokine profiles and effector functions, such as Th1 (expressing IL-2, IFN-γ, and TNF-α), Th2 (expressing IL-4, IL-5, and IL-13) and Th17 (expressing IL-17 and IL-22) (Bodles and Barger, 2004; Kaiko et al., 2008; Mosmann et al., 1986; Mosmann et al., 2005; Wilson et al., 2009). According to the Th1/Th2 paradigm, cytokines secreted by Th1 and Th2 antagonize each other to the extent that Th1 and Th2 development are considered mutually exclusive (Mosmann and Coffman, 1989). Recently, following the discovery of a new lineage of IL-17 producing effector T cells (Th17) which exhibit unique effector functions distinct from Th1 and Th2 cells has redefined the Th1/Th2 paradigm (Bettelli et al., 2006). Through expression of IL-17A, Th17 cells are able to amplify clearance of pathogenic cell types via increased cell-mediated immunity by T cells, antibody production by B cells as well as increase production of antimicrobial peptides such as defensins and S100 proteins, proinflammatory cytokines and chemokines, as well as matrix metalloproteinases in a variety of cells including fibroblasts, endothelial cells, and epithelial cells (Iwakura et al., 2008). In addition to involvement in mutual immuneregulation, Th1, Th2 and Th17 regulate mononuclear phagocytes, B lymphocytes and polymorphonuclear cells, respectively. Thus such regulation functions exhibit several common characteristics including redundancy, pleiotropy, synergy, and antagonism (Korn et al., 2009). This level of activity must be tightly regulated, lest these T cells become over-stimulated and hyper-activated leading to dysregulation, pathological sequelae, or overt autoimmune disease. In order to avoid detrimental effects, new homeostatic balances must be attained with shifts in Th1/Th2/Th17 predominance within disease progression (Kaiko et al., 2008).

Since interactions along the neuroendocrine-immune axis are analogous to a scale-free network, rather than a single-direction axis, communication is controlled via using the soluble molecules of each system (neurotransmitters, hormones and cytokines) as common signals (Fabris et al., 1995; Miller, 1998). Here, we address only how immune system affects the CNS in both in both maintenance of homeostasis and in disease.

In the healthy brain, CD4+ T cells are indispensable for homeostasis; whereas, during disease Th1, Th2 and Th17 cells play different roles in neuroprotection and neurodestruction (Chen et al., 2008a). Signaling by innate immune cells differentially activated by recognition of various pathogenic types or different traumas to the brain, different effector T cells can dictate the functional potential for orchestrating pathogen clearance and wound repair. During this process, Th1 and Th17, as producers of pro-inflammatory cytokines, directly contribute to neuroinflammation by secreting IL-1, IL-6, IL-17, TNF-α and IFN-γ, as well as indirectly enhance microglia-mediated neurotoxicity by up-regulating the release of reactive oxygen species (ROS) and nitric oxide (NO) from microglia (Weiner, 2008). Th2, as producers of anti-inflammatory cytokines, up-regulate the release of insulin-like growth factor-1 (IGF-1) from microglia and enhance microglia-mediated neuroprotection (Appel et al., 2008). Moreover, recent studies show that effector T cells could enhance neuroinflammation and accelerate neurodegeneration in the MPTP-induced PD model and the HIV-1/VSV-infected HIVE model (Benner et al., 2008; Liu et al., 2009; Reynolds et al., 2007b). These observations have led to the theoretical basis to skew the neuroimmune response away from a pro-inflammatory cytokine profile toward an anti-inflammatory cytokine pattern as a therapeutic strategy for neurodegenerative diseases.

6. Regulatory T cells and neurodegenerative diseases

Natural occurring regulatory T cells (Tregs) are characterizied by several constitutively expressed markers, including CD4, CD25, CD62L, CD103, CD152, glucocorticoid-induced

tumor necrosis factor receptor (GITR), latency-associated peptide (LAP), the forkhead homeobox domain P3 (FoxP3) transcription factor (Battaglia et al., 2003; Chen et al., 2008a; Igarashi et al., 2008; Nishizuka and Sakakura, 1969). FoxP3 transcription factor is essential for the phenotype and function of Tregs (Huehn et al., 2009; Sakaguchi, 2004). A primary role of Tregs is to provide immune tolerance to self (Onishi et al., 2008; Sakaguchi, 2004). Self-tolerance is achieved and maintained by "recessive" and "dominant" mechanisms (Sakaguchi, 2004; von Boehmer, 2003). In recessive mechanisms, self-reactive lymphocytes are programmed to die by apoptosis when exposed to self-antigen at an immature developmental stage in the thymus (T cells) and bone marrow (B cells); a phenomenon referred to as clonal deletion. Other recessive mechanisms may render the cell functionally inactive (anergic) after exposure to self-antigen. In dominant mechanisms, T cells actively inhibit activation and expansion of aberrant or over-reactive lymphocytes (active suppression), in particular other types of T cells. Evidence now indicates that each adaptive immune response involving T or B effector cells yields an appropriate regulatory response to maintain balance between the two populations. This is seemingly critical for proper control of adaptive immune responses, both in quality and magnitude, and for the establishment or breaking of tolerance to self and non-self antigens. Indeed the absence of Tregs early in postnatal development of mice results in systemic multi-organ autoimmunity, in "recessive" self-tolerance,

Studies on the immunological synapse indicate that while Teffs are induced through cell-cell contact at the synapse in the context of soluble mediators or signals (Huppa and Davis, 2003), Tregs inhibit Teff activation at the immunological synapse through via cell-cell contact, secretion of immunosuppressive cytokines such as IL-10 and TGF-β, and direct effector cell killing. Increasing evidence indicate since Tregs operate primarily at sites of inflammation, all their diverse mechanisms are available to modulate immune reactions under variable inflammatory conditions. Their mechanistic complexity and diversity evolves from diverse tasks performed by various Treg cell subsets in different stages of the immune reaction. (Huehn and Hamann, 2005). However, in different disease states, Treg function results in vastly different outcomes, wherein autoimmunity and neurodegeneration Tregs may protectively attenuate inflammation; whereas, in infectious and neoplastic disease Tregs may suppress the immune response necessary to eliminate foreign entities (Alyanakian et al., 2003; Belkaid et al., 2002; Ghiringhelli et al., 2004; Sakaguchi et al., 2001; Smyth et al., 2001; Viglietta et al., 2004; von Herrath and Harrison, 2003; Wang et al., 2004). Thus, Treg function for neuroregulation may be considered a double-edged sword whereby as a regulator of innate immunity or microglial-mediated neurotoxicity, which inhibits neuroinflammation, may also prevent the necessary clearance of misfolded proteins, neuronal debris, or viral infected reservoirs.

Nonetheless, whether Tregs are beneficial or detrimental in HIV-1 infection has not been entirely resolved. Some have suggested a detrimental role for Tregs since they suppress the immune response to HIV and allow HIV-1 progression (Seddiki and Kelleher, 2008; Tenorio et al., 2009), however others suggest a more beneficial role for Tregs due to their ability to suppress chronic immune activation and neuroinflammation, both main initiators of neuronal pathology in HIV (Seddiki and Kelleher, 2008). For example, SIV-infected natural hosts, sooty mangabeys (SM) do not develop AIDS, because they maintain substantive Treg levels and show limited immune activation while simian immunodeficiency virus (SIV)-infected Asian rhesus macaques (RM) readily progress to AIDS and poorly suppress chronic immune activation (Klatt et al., 2008; O'Connell and Siliciano, 2008; Pereira et al., 2007; Seddiki and Kelleher, 2008; Silvestri et al., 2007). Thus, differences in clinical outcome in disease-resistant SM and disease-susceptible RM may be linked, in some manner, to Treg responses, however this is not absolute. Indeed, the numbers of peripheral Tregs in chronically SIV-infected SM are maintained while a significant loss occurs in chronically SIV-infected RM. Further works, however, showed correlations between plasma viral load and the level of Tregs in SIV-infected

RM, but not SM. Treg-depleted PBMC from RM led to a significant enhancement of $CD4^+$ and $CD8^+$ T-cell responses to SIV peptides, there was no detectable T-cell response to the same pool in Treg-depleted cells from SIV-infected SM (Klatt et al., 2008; O'Connell and Siliciano, 2008; Pereira et al., 2007; Seddiki and Kelleher, 2008; Silvestri et al., 2007).

Using dialectic views, it is possible that Tregs play divergent roles early in infection than late in disease. Early in infection, potent HIV-specific immune responses are suppressive, whereas later in infection, Tregs suppress the chronic immune activation (Klatt et al., 2008; O'Connell and Siliciano, 2008; Pereira et al., 2007; Seddiki and Kelleher, 2008; Silvestri et al., 2007). Taken together these results suggest new theories on pathogenesis of HIV diseases and new strategies on HIV/AIDS therapies such as a generalized immune over-activation hypothesis versus a tolerance induction strategy (Bourinbaiar and Abulafia-Lapid, 2005; Brenchley, 2006; Brenchley et al., 2006; Grossman et al., 2006; McMichael, 2006; Mehandru et al., 2004; Neutra and Kozlowski, 2006; Pearson, 2004; Rizzardi et al., 2002). Most interestingly, the conventional immunotherapeutic approaches aimed at enhancing the immune response against HIV have repeatedly failed when applied in clinical practice, while clinical benefit has been invariably associated with usage of vaccines that act in accord with the principles of alloimmunization. Thus immunotherapeutic strategies incorporating alloimmunization, which primarily induce tolerance rather than immune activation, might better yield clinical outcomes in HIV/AIDS (Bourinbaiar and Abulafia-Lapid, 2005; Bourinbaiar et al., 2006).

Since chronic neuroinflammation seemingly plays a demonstrable role in progression of neurodegeneration, Tregs, having the capacity to attenuate inflammation, represent an attractive therapeutic target in neurodegenerative disorders (Kipnis et al., 2004; Liesz et al., 2009; O'Connor and Anderton, 2008; Planas and Chamorro, 2009; Reynolds et al., 2007b). Mechanisms by which Tregs attenuate neuroinflammation include suppression of Teff activation and induction of Teff apoptosis (Grossman et al., 2004a; Grossman et al., 2004b; Pandiyan et al., 2007; Scheffold et al., 2007). Recent data also demonstrate that Tregs provide neuroprotective activity by upregulation of brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), downregulation of pro-inflammatory cytokines and ROS production, as well as direct induction of apoptosis in α-synuclein activated microglia and HIV-1/VSV infected macrophages (Liu et al., 2009; Reynolds, 2009). These findings present Tregs and Treg function in a new light relative to neurodegeneration, whereby multiple and new regulatory mechanisms have been determined (Figures 1 and 2). Tregs use not only Fas/FasL pathways, but also perforin/granzyme pathway to destroy target cells (Grossman et al., 2004a). Additionally, Tregs utilize other immunosuppressive mechanisms including production of IL-10 and TGF-β (O'Connor and Anderton, 2008), downregulation or aggregation of microglial MHC and CD80/CD86 molecules (Onishi et al., 2008; Reynolds, 2009), hydrolysis of ATP released by necrotic cells and synthesis of cAMP by highly active adenylyl cyclase (Bopp et al., 2007). Moreover, Tregs also induce the transformation of brain MP from M1 phenotype to M2 phenotypes as an effective mechanism to attenuate neuroinflammation (Tiemessen et al., 2007) (Figure 2).

In models that recapitulate the effects of Tregs on α-synuclein stimulated microglia in early asymptomatic and later overt disease stages in PD, Tregs have been shown to exhibit distinct functions (Banerjee et al., 2008; Reynolds et al., 2007b; Reynolds, 2009). Co-culture of microglia with Tregs prior to stimulation (early asymptomatic stage) converts a neurotoxic microglial phenotype to neuroprotective by inhibition of oxidative stress and diminution of cathepsin activity. On the other hand, co-culture of Tregs after microglial stimulation (late, overt disease) induces microglial apoptosis by upregulation of CD95 ligand and increased caspase-3 activity. Proteomic studies revealed that Tregs alter the α-synuclein-stimulated microglial proteome whereby modulated cellular proteins were associated with metabolism, migration, phagocytosis, protein transport and degradation, redox biology, and cytoskeletal

and bioenergetic cell functions (Reynolds, 2009). These data support the importance of adaptive immunity in the regulation of PD-associated microglial inflammation and suggest a novel hypothesis for Treg regulation of microglial functions during the asymptomatic and overt disease stages in PD. During early, asymptomatic PD, regulatory adaptive immune responses attenuate microglial activation and neuroinflammatory responses, as well as control ROS and retard degenerative activities and disease progression.. Tregs at this stage, modulate microglia to be actively phagocytic and produce a broad spectrum of regulatory factors that maintain CNS homeostasis and limit α-synuclein accumulation. In the overt stage, regulatory immune responses break down, leading to hyperactive Teff function, loss of neuroimmune surveillance. Moreover, as aging is a major risk factor for PD, microglial senescence may lead to functional deficiency and chronic microgliosis. Treg mechanisms at this stage would then preferentially favor induction of microglial programmed cell death over anti-inflammatory activity (Reynolds, 2009).

In recent studies in models of HIVE, Tregs suppress ROS production and pro-inflammatory cytokine secretion by HIV-1 infected macrophages (Liu et al., 2009). In addition, Tregs reduce virus replication and induce macrophage apoptosis. Beneficially, this would inhibit macrophage activation and migration, decrease viral load, and destroy viral reservoirs in HIV-1 infected individuals. Furthermore, extended preservation of Tregs in the peripheral blood of HIV-1 infected elite suppressors (those that maintain CD4+ counts and controlled viremia) has been suggested as one mechanism to control progression of HIV-1 infection (Chase et al., 2008) (Figure 1). Based on those findings, upregulation of Treg numbers or Treg function represent an attractive strategy for therapeutic vaccine study in HIV-1 infection. In HIVE, adoptive transfer of Tregs attenuates astrogliosis and microgliosis with concomitant neuroprotection, upregulation of neurotrophic factors, downregulation proinflammatory cytokines, oxidative stress, and viral replication (Liu et al., 2009). Additionally, co-culture of human peripheral blood monocytes derived macrophage (MDM) with Tregs induces accelerated MDM cytotoxicity upon homotypic cell aggregation and fusion, while co-cultivation with Teffs enhances MDM activation with increased activated stellate and elongated morphologies (data from our laboratory).

Using the G93A-SOD1 transgenic mouse model of ALS, adoptive transfer of Tregs delays onset of neurological symptoms, while Teffs increases the latency between onset and entry into late stage, although both Tregs and Teffs delay the loss of motor function and extend survival (Banerjee et al., 2008). Although the precise mechanisms for this dual protective role of both effector and regulatory T cell populations has not been fully elucidated, subsequent studies support the observation that CD4+T cells have a protective role in the etiology of ALS (Appel, 2009) and supports an adaptive immune abnormality in CD4 T cell function in the G93A SOD1 transgenic mouse model (Appel, 2009; Banerjee et al., 2008).

In addition, one study indicated that Tregs only in the CNS, not in the other secondary lymphoid organs, retain a remarkable proliferative capacity which could drive accumulation of resident Tregs, but not peripheral Tregs, in inflamed CNS (O'Connor and Anderton, 2008). In light of those findings, passive transfer or active induction of Tregs is a potential attractive strategy for therapeutic intervention of neurodegeneration, whereby reactive neurotoxic T cell subpopulations are converted to anti-inflammatory and neurotrophic..

7. CTL and neurodegenerative diseases

CD8+ CTLs are well known for killing of target cells, which include viral-infected cells, tumor cells and hyperactivated cells. CTLs kill targets cells via three non-mutually exclusive pathways, which utilize perforin/granzyme, Fas/FasL, and TNF/TNFR. Few CTLs are found in normal CNS during immune surveillance, however under pathological conditions such as

stroke, tumor, infection, neurodegeneration, or autoimmunity increased numbers of peripheral CTL proliferate and accumulate in and around brain lesions. Whle seemingly necessary for insult clearance, excessive CTL numbers or CTL activity, as found in multiple sclerosis, could be deleterious (Neumann et al., 2002).

8. Immune-based pathways for neurodegeneration

Accumulating evidence indicates that the kynurenine pathway (KP) and quinolinic acid (QA) play a role in neurodegeneration (Moresco et al., 2008) possibly via mechanisms of excitotoxicity and astrocytic apoptosis (Dantzer et al., 2008). Indolamine 2, 3-dioxygenase (IDO), which converts tryptophan into kynurenine (Ghiringhelli et al., 2004), was first recognized as a vital immunomodulatory enzyme in immunosuppression (Dantzer et al., 2008; Kwidzinski and Bechmann, 2007). Its role IDO in the brain has more recently been highlighted through characterization of the QA pathway, for which QA is a product of the KP. In addition, IDO is found to be highly inducible by pro-inflammatory cytokines, including IFN-γ and TNF-α (Dantzer et al., 2008; Kwidzinski and Bechmann, 2007), which augments IDO with exacerbatory effects. As a result, IDO has evolved as a novel target for therapeutic intervention of neurodegeneration as well as depression.

Arachidonic acid (AA), as the other key metabolite involved in neurodegeneration, is the product of phospholipases A2 (PLA2) hydrolyzation of membrane phospholipids and is the precursor for various proinflammatory mediators, including prostaglandins, leukotrienes, and thromboxanes. Under homeostatic conditions, PLA2 regulation provides balanced AA conversion into proinflammatory mediators and AA reincorporation into the membrane. Loss of strict control of PLA2 activity under disease conditions, yields the disproportionate production of proinflammatory mediators which exacerbates neuroinflammation and neurodegeneration in AD, ALS and MS (Farooqui et al., 2006; Pinto et al., 2003; Sun et al., 2004). Treatment with PLA2 inhibitors has proven effective in animal models suggesting another attractive therapeutic candidate in neurodegenerative diseases (Farooqui et al., 2006).

The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) (Tansey et al., 2007) are two important mechanisms involved in elimination of intracellular pathogens and misfolded proteins, and antigen presentation by MHC II molecules (Pan et al., 2008). Alteration of UPS or autophagy diminishes protein degradation and leads to abnormal protein aggregation; a principal histopathological finding in neurodegenerative diseases. Thus, dysfunctional UPS and ALP, which play pivotal roles in protein clearance mechanisms under homeostatic conditions and misfolded protein aggregation in the pathogenesis of neurodegeneration, will provided another promising target for therapeutic intervention (Mayer et al., 1996; Mayer et al., 1994; Pan et al., 2008).

9. Conclusion

We hypothesize that regardless of the initiating etiological insult or affected brain area particular for each neurodegenerative disorder, a “two-stage” neuroinflammatory pathway is a common element in neuropathogenesis and disease progression. Early, during asymptomatic stages of disease, regulatory T cells maintain, in large part, control over neuroinflammation, and although unable to totally inhibit disease progression, secondary neurodegeneration due to over-active neuroinflammation is maintained at minimal levels. Phagocytic microglia engulf and digest neuronal debris and misfolded proteins with occasional inflammatory events, but inflammation is relatively contained. With disease progression, regulatory control is gradually lost, resulting in increased microglial hyperactivity and neurotoxicity leading to greater insult and secondary neurodegeneration that is more characteristic of overt disease during the symptomatic stage. Thus therapeutic strategies that enhance regulatory control over

hyperactive immune responses either through suppression of microglial or Teff functions would target the neuroinflammatory component commonly associated with neurodegenerative disorders.

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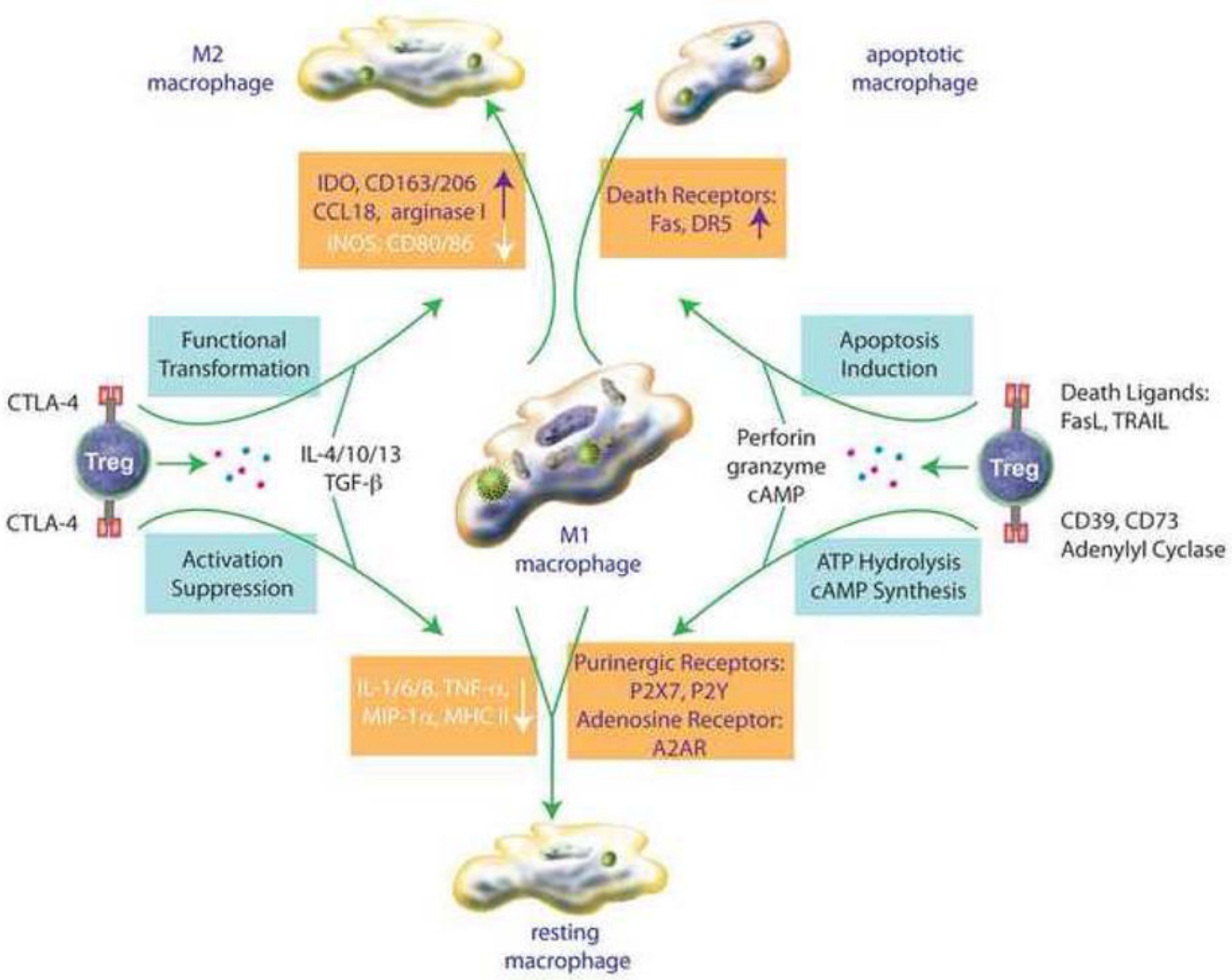

Figure 1.

The potential for multifaceted roles of Treg in the immunoregulation of the HIV-1 infected macrophage. Such roles may include activation-suppression, phenotypic modulation, functional transformation or induction of apoptosis and may substantively affect the onset and tempo of neurodegeneration in the setting of HAND.

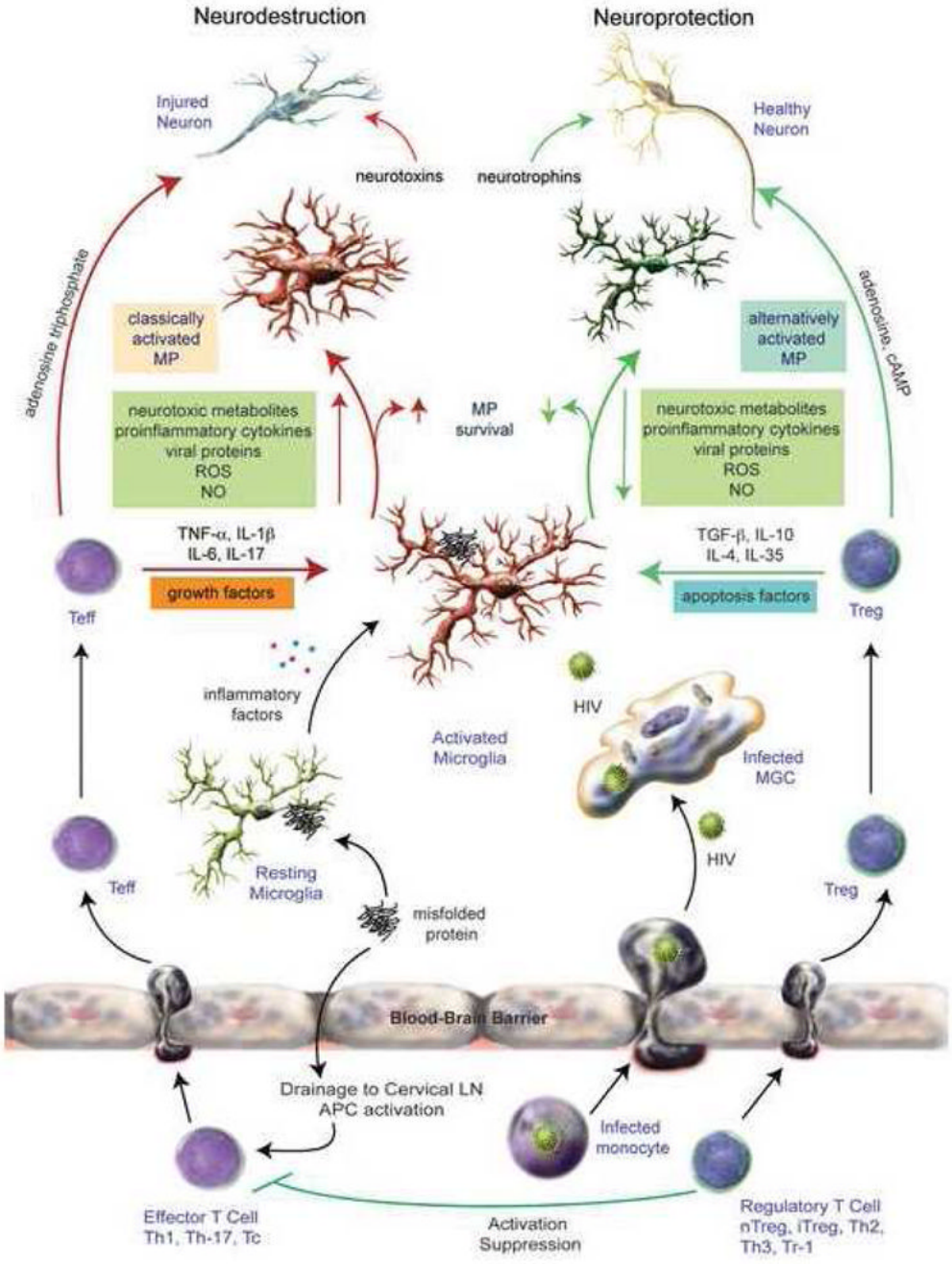

Figure 2.

The multifaceted roles of Treg and Teff in neurodegenerative disorders. For neurodegenerative disease (HAND, PD, AD, ALS), Teff and Treg exert opposing influences on neuronal function and speeding neurodestruction *or* neuroprotection, respectively. However, in early stage disease immunoregulatory control responses are operative and initiated by Treg to modulate MP homeostatic function and promote neuronal integrity. However, as disease progresses Teff up-regulate neurotoxic molecules and exacerbate MP activation and dysfuction, while Treg attenuate these neurotoxic responses. Treg modulate neuronal survival and function and could occur through changes the phenotype of the M1, pro-inflammatory brain MP to an M2

phenotype. The latter is an alternatively activated macrophage that possesses anti-inflammatory and potential neuroprotective functions.