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A Perspective on Roles Played by Innate and Adaptive Immunity in the Pathobiology of Neurodegenerative Disorders

Howard E. Gendelman and **R. Lee Mosley**

Department of Pharmacology and Experimental Neuroscience, Center for Neurodegenerative Disorders, University of Nebraska Medical Center, Omaha, Nebraska, 68198

Abstract

Aberrant innate and adaptive immune responses are neurodegenerative disease effectors. Disease is heralded by a generalized but subtle immune activation orchestrated by the release of extracellular prion-like aggregated and oxidized or otherwise modified proteins. These are responsible for an inflammatory neurotoxic cascade. The perpetrators of such events include effector T cells and activated microglia. What ensues are Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis and stroke with changed frequencies of effector T cell and reduced numbers or function of regulatory lymphocytes. The control of such immune responses could lead to new therapeutic strategies and the means to effectively combat a composite of diseases that have quite limited therapeutic options.

Alzheimer's and Parkinson's disease (AD and PD), amyotrophic lateral sclerosis (ALS) and stroke are devastating neurodegenerative disorders with few effective therapeutic options (Sibon et al., 2015). Diseases are linked, in measure, with neuroinflammation and disordered immunity (Anderson et al., 2014). All affect the central nervous system (CNS) and show, in whole or part, innate glial activation with altered frequencies of effector and regulatory T cells (Teff and Treg) in numbers and/or function (Benner et al., 2004; Reynolds et al., 2007a; Reynolds et al., 2007b; Reynolds et al., 2008; Beers et al., 2011; Zhao et al., 2013; Chan et al., 2015; Hooten et al., 2015; Koronyo et al., 2015; Gesuete et al., 2016). Of these CNS disorders, AD is the most common and perhaps most devastating (Zhao et al., 2014). Clinical disease manifestations are marked by abnormal cognitive function whereby progression to dementia is both profound and devastating. Pathologically clinical neurological features are associated by deposition of extracellular amyloid-beta protein (Aβ) and the formation of neurofibrillary tangles (Lashley et al., 2015). Immunosenescence and inflammation contributes to AD pathogenesis (Candore et al., 2010; Di Bona et al., 2010; Martorana et al., 2012; Michaud et al., 2013; Castelo-Branco and Soveral, 2014; Fulop et al., 2015). Systemic immunity affects disease pathogenesis by altering the phenotype of microglia (Heneka et al., 2015; Latta et al., 2015; Lucke-Wold et al., 2015; Mhatre et al., 2015; Yamada, 2015; Zhang and Jiang, 2015). As both Teff and Treg were theorized to play a crucial role in maintaining systemic immune homeostasis, the preservation of these cells' immune functions is likely to control disease tempo (Saresella et al., 2010; Toly-Ndour et

Corresponding author: Howard E. Gendelman, M.D., Department of Pharmacology and Experimental Neuroscience, 985880 Nebraska Medical Center, Omaha, NE 68198-5880 USA; hegendel@unmc.edu; phone: 01-402-559-8920; fax: 01-402-559-3744.

al., 2011; Yang et al., 2013; Schwartz and Baruch, 2014; Baruch et al., 2015; Wang et al., 2015). In support of this idea, transplantation of splenocytes acquired from young mice without CNS disease not only prevented AD, but also improved spatial learning and memory in APPswe/PSENldE9 transgenic animals (Wang et al., 2015). Young splenocytes enhanced Aβ clearance, reduced gliosis astrogliosis and increased growth factor concentrations. In contrast, splenocytes from older transgenic animals show changed Treg numbers, increased microglia and astrocytes, increased deposition of Aβ plaques, and diminished behavioral function. These results suggested deficits in immune cell function, not simply number affect the signs and symptoms of AD in mice, and that a functional immune system is not only required for optimal cognition, but may also be harnessed for therapeutic gain. In further support for this idea is that transplantation of immune modulatory mesenchymal stem cells into the AD mouse hippocampus can ameliorate disease progression. The observations made provide further support for the importance of immune control in AD pathobiology. Notably, systemic transplantation of purified autologous splenic Tregs into APPswe/PS1dE9 mice ameliorates impaired cognition and reduces plaques and soluble Aβ (Yang et al., 2013). The numbers of activated microglia and accompanying pro-inflammatory responses are also reduced. In all, these results demonstrated that systemic Treg administration could be an effective AD treatment. Divergent results were observed in a replicate study. Using the AD 5XFAD mouse model that mirrors human neuropathological and behavioral changes as well as motor disease, spinal cord axonopathy and intraneuronal Aβ studies of immune modulation were performed. 5XFAD also shows neuron loss. Herein, transient depletion of Foxp3+ Tregs or pharmacological inhibition of Treg activity was associated with amyloid-β plaque clearance, reduced neuroinflammatory response and cognitive decline reversals (Baruch et al., 2015). Such Treg depletion was also shown to affect the choroid plexus and as such affect immune cell CNS trafficking that included monocyte-derived macrophages and Tregs to plaque sites. The work suggests that Treg-mediated systemic immunosuppression may be an opposite treatment strategy for AD. More likely is that both effector and regulatory arms for the immune system need be operative to elicit a therapeutic response and while breaking immune tolerance by depleting Treg could speed the clearance of plaques the need to tissue repair and dampening of inflammatory responses will come necessary in any therapeutic strategy. It should be noted that breaking immunological tolerance in a Phase II clinical trial using a vaccine combination of Aβ and QS21, a strong Th1-polarizing adjuvant, resulted in cessation of the trial due to a significant portion of patients developing meningoencephalitis with T cell infiltrates (Ghochikyan et al., 2006). It was later found that PBMCs of patients from that trial, stimulated in vitro with Aβ produced predominantly proinflammatory Th1 responses (Pride et al., 2008).

Similar immune modulation strategies have shown to be operative in PD (Benner et al., 2004; Mosley et al., 2006; Reynolds et al., 2007a; Reynolds et al., 2007b; Benner et al., 2008; Reynolds et al., 2008; Reynolds et al., 2009a, b; Mosley and Gendelman, 2010; Reynolds et al., 2010; Mosley et al., 2012; Saunders et al., 2012; Deleidi and Gasser, 2013; Dexter and Jenner, 2013; Kosloski et al., 2013; Chao et al., 2014; Allen Reish and Standaert, 2015). Indeed, PD highlights, perhaps more than other neurodegenerative disorders, the importance of inappropriate T cell responses in CNS disease pathogenesis. Notably, on the

one hand effector immune responses were shown to exacerbate neurotoxic responses and on the other regulatory activities lead to neuroprotective outcomes. The temporal and spatial mechanisms of these two responses were studied in the setting of active disease by our own laboratories and others. Indeed, the effector immune responses herald neurodegeneration and may be initiated outside the CNS as a consequence of systemic accumulation of cell-specific stimuli and or nitrated, aggregated proteins where α-synuclein dominates. The migration of antigen-specific CD4+ T cells from the periphery to the CNS generates immunocyte-microglial activities that perpetuate neuroinflammation and affect neuronal survival. The destructive or protective mechanisms of such interactions are linked to time, numbers, and function of a dominant Teff or Treg response. The final result is altered glial and neuronal functions that affect disease tempo. Recently investigators posited that transformation of immune responses could permit potential novel therapeutic pathways that retard disease progression (Hutter-Saunders et al., 2011; Ha et al., 2012). To such ends, we will soon complete a double blind phase I clinical study that uses granulocyte macrophage colony stimulating factor to transform effector to regulatory T cells with the idea that such an immune response would lead to neurological improvements in motor, gait and behavioral symptoms of human disease. The results of this study will come available early in 2016.

ALS while a very different neurodegenerative disorder in signs and symptoms also shares immune regulatory activities as part of its pathobiologic signature (Beers et al., 2011; Zhao et al., 2013; Hooten et al., 2015). ALS is notably a fatal neurodegenerative disease characterized by upper and lower motoneuron injury and death. Mutations in the superoxide dismutase 1 (SOD1) gene, leads to a familial form of the disease, and is commonly employed to generate transgenic mice for studies of disease pathobiology and developmental therapeutics (Vucic and Kiernan, 2009; Nassif et al., 2010; Ince et al., 2011; Peters et al., 2015). Animals that overexpress human mutant SOD1 (mSOD1) exhibit a motoneuron disease that is phenotypically similar to that is seen pathobiologically in human ALS including neurodegeneration and neuroinflammation. The latter is typified by the activation and proliferation of microglia and detectable T cell infiltration into the spinal cord and brain. While neuroinflammatory responses are commonly viewed, as a pathologic consequence of neuronal death, there is now considerable evidence that manipulation of immune responses substantively alters neuronal survival. Phenotypic alterations of microglia function in mSOD1 mice early in disease can predict the disease course. Such phenotypic changes can be orchestrated by T cell signals. During advanced disease, microglia evolve into an inflammatory neurotoxic phenotype, and as such, its transformation affects disease and consequent therapeutic outcomes (Hooten et al., 2015).

A number of mechanisms for motor neuron injury has been implicated in ALS based a wide range of genetic disease causes for familial disease. In the mSOD mice, motor neurons die based on cell-to-cell interactions between motor neurons, glia and circulating immunocytes (Zhao et al., 2013). There are two disease stages one is neuroprotective and the other, a later one, neurotoxic and degenerative. During early phases of disease progression, the immune system protects the motor neurons with predominant M2 microglia and regulatory T cell dominance (Henkel et al., 2009; Liao et al., 2012; Chiu et al., 2013; Evans et al., 2013; Zhao et al., 2013; Nikodemova et al., 2014; Tada et al., 2014; Hooten et al., 2015). This heralds a neuroprotective anti-inflammatory signature to curb disease and provide control for

neurodegenerative pathways. In the second stage, motor neuron injury dominates as does a change in phenotype of microglia from the M2 to an M1 with reductions in Treg numbers and function, and the emergence of effector neurotoxic proinflammatory lymphocytes. In rapidly progressing ALS patients, as in transgenic mice, immune-mediated neurotoxicity becomes the disease signature. To these ends, recruitment of immunoregulatory cells to the diseased spinal cord in ALS, needed for amelioration of the pathology, can be enhanced by transiently affecting peripheral immunity to myelin antigens. It is thought that enhancing peripheral Treg function actually worsens CNS pathology and that enhancing a proinflammatory state in the periphery is needed to "open a gate" through the choroid plexus. However, bench to bedside studies in regards to Treg functional activities for temporal and special relationships to disease challenge this concept. Indeed, the majority of papers now in the literature provide a more direct role for the neuroprotective function of Tregs in both transgenic ALS mouse and for human disease (Henkel et al., 2009; Beers et al., 2011; Liao et al., 2012; Zhao et al., 2013; Hooten et al., 2015).

Thus, without a doubt, mounting evidence indicates that adaptive immunity can modulate innate microglial activation and consequent disease progression. This is a component not only found in ALS, but also for most prevalent neurodegenerative diseases. The switch on how, when and under what circumstances neurotrophic activities evolve to neurotoxic outcomes is not certain. Indeed, how this occurs remains in some debate, although prevailing evidence supports that idea that aggregated, oxidized and nitrated proteins enable a break in immune tolerance with the emergence of effector neurotoxic T cells. Indeed, evidence abounds that immunological factors are linked to the pathogenesis of ALS. Although associated in largest measure to late disease, T cells appear in spinal cord tissue of affected patients and also in diseased mice. T-cell cytokines that include, but not limited to, interferon gamma (IFN-γ), interleukine-2 (IL-2), -3, -4 and -5, are increased in the spinal cords of mSOD1 mice, and IFN-γ is elevated in ALS patients' sera (Su et al., 2013). Recent studies have clearly established a neuroprotective role of adaptive immunity, or more specifically for Tregs (Anderson et al., 2014). There is also clear evidence of reduced proliferative abilities of T cells as well as a global dysregulation of lymphocyte functions that occur during disease progression in mSOD1 mice (Hooten et al., 2015). This is associated with impaired splenic lymphocytes in mSOD1 mice. A lack of functional T cells is highlighted by prior crossing experiments with knockout mice (*Rag*$^{-/-}$, *Cd4*$^{-/-}$ and *Tcr*$^{-/-}$). Each has been shown, more or less, to accelerate motor neuron degeneration and to diminish survival. T cell depletion is linked to microglial phenotypes including levels of activation and production of neurotrophic factors. Interestingly, adoptive transfer of activated T lymphocytes is protective to mSOD1 mice supporting a beneficial role for T cells in regulating microglial cell activation and neuronal survival in ALS. Systemic immune activation is observed in ALS patients, as shown by examinations of T cell subsets in ALS patients. CD8+ cytotoxic T cells and natural killer (NK) T cells are increased significantly during ALS. Importantly, Treg numbers are reduced significantly and correlate negatively to disease severity. It is theorized that the higher number of CD8+ and NK T cells emerge as a result of a reaction to an endogenous pathogen, protein or to a changed immune microenvironment. A most likely explanation of such clinical findings is altered phenotypes

of T cells that yield a neurodestructive or neuroprotective outcome are influenced by the balance of Teffs and Tregs, respectively..

Interestingly, there is also reduced thymic function and Treg number in ALS patients. In mSOD1 mice, adoptive transfer of Tregs ameliorates disease. By affecting endogenous CD4+ T cells through surgical castration, weight change, disease onset, and progression were examined concurrently with the numbers of CD4+, CD8+ and CD4+FoxP3+ Tregs by flow cytometry. Motor neuron counts, glial cell activation and androgen receptor expression in the spinal cord were investigated using immunohistochemistry and Western blotting. Castration significantly increased thymus weights and total CD4+ T cell numbers in mSOD1 mice, although Treg levels were not affected (Thomas and Sharifi, 2012). Despite this, disease onset and progression were similar in castrated and sham mSOD1 mice. Castration did not affect motor neuron loss or astrocyte activation in the spinal cords of mSOD1 mice. While microglial activation was reduced, increasing thymic function and CD4+ T cell number by castration resulted in no clinical benefit in the mutant SOD1 mice. This lack of response likely reflected the inability to stimulate neuroprotective Treg responses in these animals. While castration diminished spinal cord M1 microglial responses, such induced-alterations of immunity and its consequences for spinal cord disease may be necessary, but not sufficient, to elicit clinical improvement and motor neuron sparing. Other functional therapeutic activities of Tregs will need to await further research.

Parallel immune responses appear operative during stroke but not without some controversy (Gauberti and Vivien, 2015; Na et al., 2015; Schuhmann et al., 2015; Veltkamp et al., 2015). While effector T cells are known to enhance brain tissue damage during ischemic stroke, a role-played by Treg in disease remains, in part, under some contention. This again as is operative for other neurodegenerative diseases may be linked to temporal immune responses.

Recent studies applied anti-CD28 antibody-mediated expansion of Treg then assayed stroke outcomes, thrombus formation and immunocyte brain infiltration into affected tissue regions. This analysis was done following middle cerebral artery occlusion. One report showed that Treg expansion enhanced stroke size and worsened functional outcomes by leading to increases in thrombus formation. In sharp contrast another report also measuring cerebral ischemia after blockade of the middle cerebral artery in mice showed favorable disease outcomes by Treg expansion. This was determined, by infarct volumetric and behavioral testing. Brain-infiltrating leukocyte subpopulations were assessed by flow cytometry up to seven days after middle cerebral artery occlusion and showed reduced infarct size and attenuated functional deficits. Mice with anti-CD28 induced increased numbers of Treg as shown by spleen and brain examinations and functional tests, demonstrated cell migration and accumulation into affected brain regions including the peri-infarct area. More than 60% of brain's Tregs produced interleukin-10 and attenuated inflammatory responses with improved clinical outcomes. The differences between the two studies could reflect timing of Treg function on disease, whereas early in the course of damage, effector cells predominate in disease control by enhancing scavenging and clearance functions in acute injury, while later anti-inflammatory and subsequent tissue "healing" responses dominate in control of disease associated events.

Our own laboratory's efforts remain focused on harnessing immune pathways for therapeutic gain in neurodegenerative diseases. The cellular players involved in destructive neuroinflammation include, most notably, microglia and T cells and current therapeutic strategies serve to transform a neurodestructive immune phenotype to a neuroprotective one. While the suppression of neurotoxicity highlights a singular goal of rescuing neuronal demise against progressive neurodegenerative activities, it is not the sole goal towards reaching clinical endpoint improvements. It is likely that a timed control of immune regulatory events is required to counteract an altered CNS microenvironment that occurs during disease. The imbalanced neuroinflammatory response associated with neurodegeneration is a single stage in a larger immune cell play. Certainly a final act of enhancing the suppressive function of Tregs and down-regulating pro-inflammatory cytokine production would serve to restore harmful inflammatory responses to a homeostatic state. However, activation of the immune system is also required to clear debris and ultimately mount such a secondary reparative response, in affect leading to sparing and restoration of damaged neurons. Overall, there is mounting and strong evidence that immune transformation can affect the pathogenesis of neurodegenerative disease and that modulation of the inflammatory response and restoring a homeostatic immune system via immunopharmacological stratetgies can lead to new opportunities to curtail all or more of these devastating nervous system disorders.

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