Neuroprotective activities of regulatory T cells

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We read with interest the opinion of Walsh and Kipnis on the roles played by regulatory T cells (Treg) in neurodegenerative diseases [1]. Although we agree that Tregs play a multifaceted complex role in disease, we hold divergent views on the importance of the cells as neuroprotective agents for central nervous system (CNS) immunity. Indeed, recent studies performed in our own laboratories demonstrated that Treg cells play critical roles in controlling the tempo of both amyotrophic lateral sclerosis (ALS) and Parkinson’s disease (PD) and that such biologic events parallel what is reported in other autoimmune and cancerous diseases [2–7]. Importantly, induction of Treg commonly leads to improved disease outcomes in animal models of human neurodegenerative disorders [3,4]. Although extrapolating from animal models to human disease is complex, the lack of effective neuroprotective therapy for ALS and PD urges the translation of Treg immunomodulatory therapeutic approaches for treatment of human neurodegenerative disorders [8].

Neuroimmunity: complex not confused

The role played by Treg in ALS and PD is not dissimilar to what is observed in peripheral wound repair. As in the periphery, the innate and the adaptive immune systems play essential roles in the maintenance of CNS homeostasis in both health and disease. The major resident innate immune cells are the microglia, which constantly survey the microenvironment through continuous extension, retraction and remodeling of their cellular processes [9]. Similar to peripheral macrophages, microglia have diverse phenotypic states spanning the spectrum from an alternatively activated [10] M2 protective phenotype producing anti-inflammatory cytokines and neurotrophic factors to a classically activated M1 toxic phenotype producing reactive oxygen species (ROS) and proinflammatory cytokines. Following tissue damage, microglia [11] undergo rapid morphological and functional activation and promote an inflammatory response that enlists the adaptive immune system in an effort to initiate tissue repair; in addition, T cells and blood-borne macrophages enter from the periphery to help restore tissue homeostasis and sustain neuronal viability.

CD4 T cell subsets also contribute to neuroprotection or neurotoxicity; Th1 and Th17 cells promote cytotoxicity, whereas Th2 and Treg promote neuroprotection. Subsets of this

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The authors have no conflicting financial interests.
heterogeneous network of CD4+ T cells may be relatively unstable, and this is especially a concern with Treg cells. Treg cells comprise two lineages: thymically derived natural Treg cells (nTreg) and peripherally derived inducible or adaptive Treg cells (iTreg), both of which are identified by their expression of FoxP3 and have significant suppressor function. However, Treg dysfunction in the presence of inflammation can abrogate suppressor function and exacerbate the damage caused by autoreactive T effector cells [7].

In divergent neurological injuries there is a common theme of immune–neural cell interactions. Neuroinflammation, characterized by activated microglia and T cells, plays a pivotal role in both neuroprotection and degeneration [2]. What has eluded scientists is how to control these critical innate and adaptive immune responses in human neurodegenerative diseases to limit toxicity and stimulate protection. In models of ALS and PD M2 microglia and T cells, notably Treg, have been observed to be neuroprotective [3,4]. A key question is how best to induce these Treg responses in human disease.

**Neurodegeneration and immunity**

What initiates neuroinflammation is not defined, but recent evidence implicates aberrant forms of misfolded brain proteins that interact with microglia and traffic to the lymphoid system, breaking immunologic tolerance and inducing adaptive immune responses [10]. Such responses generate proinflammatory Th cells, amplifying neuronal demise and the resulting parallel pathogenic pathways seen in autoimmunity [6]. Th1 and Th17 T cells contribute to neuroinflammation through molecules such as IL-1, IL-6, IL-17, TNF-α and IFN-γ, enhancing microglia-mediated neurotoxicity by upregulating the release of reactive oxygen species and nitric oxide. By contrast, Th2 and Treg, as producers of anti-inflammatory cytokines, enhance microglia-mediated neuroprotection. Thus, conversion to a neuroprotective microglial response is a therapeutic goal and an immunization strategy for ALS and PD.

**Neuroprotection and Treg**

Tregs, having the capacity to attenuate inflammation, represent an attractive therapeutic target. Tregs induce neuroprotective activity by upregulating neurotrophic factors, downregulating proinflammatory cytokines and reactive oxygen species, and directing induction of apoptosis in M1 microglia. The passive transfer of Treg from early disease stage Cu²⁺/Zn²⁺ superoxide dismutase (SOD) mutant mice showed enhancement of neuroprotective microglia and prolonged survival of the ALS mice [3]. Secretion of IL-4 among other anti-inflammatory cytokines from the administered Treg was believed to suppress the microglial neurotoxic activities. Interestingly, ALS patients in this study with more rapidly progressing disease had decreased numbers of Treg, and the numbers were inversely correlated with disease progression. These findings suggest a pivotal role for Tregs in protecting against neurodegeneration, and recent results suggest multiple and novel regulatory mechanisms are likely to be involved [3]. For example, Tregs use not only the Fas/FasL pathways but also the perforin/granzyme pathway to destroy target cells. Additionally, Tregs utilize alternative immunosuppressive mechanisms including production of IL-10 and TGF-β, downregulation or aggregation of microglial MHC and CD80/CD86
molecules, hydrolysis of ATP released by necrotic cells and synthesis of cAMP by highly active adenyl cyclase. Will harnessing Treg responses lead to an effective immunotherapy in ALS and PD? Our own data in mouse models suggest that Treg can enhance neuroprotection through interactions with microglia [5], and human studies suggest that neurotoxicity is associated with decreased Treg FoxP3 expression [3]. The major question is what signals downregulate such Treg functions and how to enhance anti-inflammatory and suppressor activity to promote neuroprotection?

**Concluding remarks**

Considerable data implicate neuroinflammation in the pathogenesis of ALS and PD models of CNS degenerative diseases. It is the ability of Treg to attenuate microglial-mediated in addition to ‘other’ effector-mediated neurotoxicities that makes its function parallel to what has been previously known and researched in the periphery and for other diseases. Harnessing the therapeutic potential of immunomodulation will mean stabilizing a regulatory population whether or not it is linked to high FoxP3 expression. Nonetheless, what remains to be seen is whether animal models and limited ex vivo human studies can be extrapolated to the whole spectrum of CNS injuries and diseases. Time will tell.

**Acknowledgments**

Funding was received from National Institutes of Health grants P20 DA026146, 5P01 DA028555-02, R01 NS36126, P01 NS31492, 2R01 NS034239, P20 RR15635, P01 MH64570, the Michael J. Fox Foundation and P01 NS43985 (to H.E.G) and NS067153 and NS048950; the Muscular Dystrophy Association; the Texas Methodist Foundation; and the Methodist Research Institute (to S.H.A).

**References**


*Trends Mol Med. Author manuscript; available in PMC 2018 April 10.*