Experimental Neurology 258 (2014) 78–90

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

Lymphocytes and autoimmunity after spinal cord injury

T. Bucky Jones *

Department of Anatomy, Arizona College of Medicine, Midwestern University, Glendale, AZ, USA

ARTICLE INFO

Article history:
Received 2 October 2013
Revised 5 March 2014
Accepted 6 March 2014

Keywords:
Autoimmunity
Spinal cord injury
Effector T-lymphocytes
B-lymphocytes
Autoantibodies
Adaptive immunity
Regulatory T-cells

ABSTRACT

Over the past 15 years an immense amount of data has accumulated regarding the infiltration and activation of lymphocytes in the traumatized spinal cord. Although the impact of the intraspinal accumulation of lymphocytes is still unclear, modulation of the adaptive immune response via active and passive vaccination is being evaluated for its preclinical efficacy in improving the outcome for spinal-injured individuals. The complexity of the interaction between the nervous and the immune systems is highlighted in the contradictions that appear in response to these modulations. Current evidence regarding augmentation and inhibition of the adaptive immune response to spinal cord injury is reviewed with an aim toward reconciling conflicting data and providing consensus issues that may be exploited in future therapies. Opportunities such an approach may provide are highlighted as well as the obstacles that must be overcome before such approaches can be translated into clinical trials.

Contents

Abbreviations: DC, dendritic cell; NK, natural killer; RAG, recombination-activating gene; BCKO, B-cell knockout; BMS, Basso Mouse Scale; BBB, Basso–Beattie–Bresnahan; Ig, immunoglobulin; CR3, complement receptor 3; FcγR, Fc gamma receptor; CsA, cyclosporin A; Treg, regulatory T-cell; nTreg, naturally occurring Treg; iTreg, induced Treg; MS, multiple sclerosis; PD, Parkinson's disease; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; EAE, experimental autoimmune encephalomyelitis; MBP, myelin basic protein; MOG, myelin oligodendrocyte protein; MAG, myelin-associated glycoprotein; OMgp, oligodendrocyte myelin glycoprotein; GluR, glutamate receptor; NgR, Nogo receptor; TBI, traumatic brain injury; APL, altered peptide ligand; SCH, spinal cord homogenate; APC, antigen presenting cell; TNF, tumor necrosis factor; TGF, transforming growth factor; IFN, interferon; IL, interleukin; TCR, T-cell receptor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; T-MBP, MBP-specific T-cells; CFA, complete Freund's adjuvant; IFA, incomplete Freund's adjuvant; VIP, vasoactive intestinal peptide; BCG, Bacillus Calmette–Guerin; FoxP3, forkhead box P3; Aβ, amyloid beta; SOD1, superoxide dismutase-1; Cop-1, Copolymer1; ROS, reactive oxygen species.

* Midwestern University, 19555 N. 59th Ave., Glendale, AZ 85308, USA.
E-mail address: bjones1@midwestern.edu.

http://dx.doi.org/10.1016/j.expneurol.2014.03.003
0014-4886/

Introduction

Over the past 15 years an immense amount of data has accumulated regarding the role of lymphocytes in the traumatized spinal cord. Despite this focus, it remains unclear whether the net impact of this response is beneficial or detrimental to the host. Indeed, it may be both. The purpose of this review is to discuss and critically evaluate the current status of the field regarding lymphocytes that accumulate within the injured spinal cord. Before modulation of the lymphocytic response can be considered clinically for its neuroprotective and regenerative potential in the context of spinal cord injury (SCI), it is imperative that we understand the complex effects lymphocytes exert on preserved or damaged tissues within the injury site.

Adaptive immunity in the injured spinal cord

Overview

The primary cellular effectors of adaptive immunity are the T- and B-lymphocytes. Lymphocyte activation requires the selective recognition of antigens via highly specific cell surface receptors (Chen and Flies, 2013; Yuseff et al., 2013), in contrast to the comparatively non-selective activation of innate immune components, which include macrophages, dendritic cells (DCs), natural killer (NK) cells and complement. T- and B-lymphocytes responsive to the same antigen interact within secondary lymphoid organs then migrate to the injury site to mount a multifaceted adaptive immune response. Lymphocytic infiltration of the injury site occurs during the first week post-injury and is maintained chronically (Ankeny et al., 2006; Beck et al., 2010; Sroga et al., 2003; Vaughn et al., 2013). Whether lymphocytes contribute to the progression or the resolution of pathophysiological events within the injury site is not well defined. Several lines of evidence implicate intraspinal lymphocytes as effectors of pathology. The use of animal models with genetic mutations in genes associated with lymphocyte development allows insight into the role of certain lymphocyte populations in SCI. Additional evidence comes from pharmacological manipulation of lymphocyte activation, function, or migration to the injury site. These data are reviewed in the next section.

Genetic manipulation of lymphocytes

In genetic models of mice and rats that lack T-cells, the absence of T-cells is generally associated with improvements in function and/or tissue preservation following SCI. In athymic (nude) rats, improvements in hind limb movements were observed after complete spinal cord transection (Potas et al., 2006). This was attributed to improved spinal reflexes rather than regeneration of descending motor systems as there were no axons present caudal to the transection site in either the nude rats or the controls. Rostral to the transection site there was improved tissue architecture associated with a reduction in activated macrophages (Potas et al., 2006).

Improvements in locomotor recovery have also been reported following contusion SCI in non-obese diabetic severe combined immunodeficient mice and following compression SCI in recombination-activating gene (RAG) 2-deficient mice (Luchetti et al., 2010; Wu et al., 2012). These mice each have a genetic mutation that affects the generation of mature lymphocytes, thus lack both T- and B-lymphocytes. In RAG2-deficient mice, locomotor recovery was associated with a greater number of monoaminergic axons caudal to the injury site which the authors attributed to regeneration (Wu et al., 2012). Although this observation may be due to an enhanced regenerative response in the absence of lymphocytes, it could also be due to a reduction in immune-mediated tissue injury when T- and B-cells are removed. Less tissue damage at the injury site would allow greater numbers of monoaminergic axons to survive and sprout in distal spinal segments. Similar results were observed in a model of peripheral nerve injury in RAG-deficient mice reconstituted with B-cells (Serpe et al., 2003). Collectively, these data suggest that T- and B-cells contribute to post-injury tissue pathology, although their relative contributions cannot be determined from these studies.

To evaluate the specific role of B-cells in post-injury neuropathology, Ankeny et al. (2009) used B-cell knockout mice (BCKO) mice that lack mature B-cells, but have a normal repertoire of T-cells. Following moderate contusion SCI, BCKO mice had improved Basso Mouse Scale (BMS) locomotor scores (Basso et al., 2006) associated with decreased lesion volume and lower levels of antibodies (immunoglobulin (Ig)M and IgG) in the cerebrospinal fluid. The presence of B220 + IgG + B-cells in the spinal cord of injured wild-type mice indicates a population of activated, mature B effector cells that had not differentiated into plasma cells (Ankeny et al., 2009). Results of this study are consistent with the studies in RAG-deficient mice described above and specifically implicate B-cells as effectors of pathology. Ankeny et al. (2009) demonstrated that the attenuation of lesion pathology and functional impairment in BCKO mice was due in part to antibodies binding to either complement receptor 3 (CR3) or Fc gamma receptor (FcγR), suggesting that the mechanism by which B-cells exert their pathogenic effects is either via activation of complement or the recruitment and activation of cells (e.g., macrophages) that express receptors for Igs (Ankeny et al., 2009). Indeed, it may be both. Complement components are present within the chronically injured spinal cord environment and contribute to pathology (Beck et al., 2010), and ligation of FcγRs modulates CR3-mediated phagocytosis (Huang et al., 2011b); also see Peterson et al., 2014-in this issue). The interaction of these two receptors likely plays an important role in modulation of the adaptive immune response.

Pharmacologic suppression of adaptive immunity

Several studies have demonstrated beneficial effects of Cyclosporin A (CsA) and tacrolimus (FK506) on locomotor recovery after SCI (Ibarra et al., 2003; Lopez-Vales et al., 2005; Lu et al., 2010; Madsen et al., 1998; McMahon et al., 2009; Nottingham et al., 2002). These agents have documented neuroprotective effects in experimental models of peripheral nerve and CNS injury, although the precise mechanisms are not well understood (Toll et al., 2011). In experimental SCI, improved functional recovery following CsA treatment was associated with increased survival of motor neurons in the spinal cord (Lu et al., 2010) and brainstem (Ibarra et al., 2003), suggesting a direct effect on neuronal survival. Cyclosporin A and FK506 also act as immunosuppressive agents that can inhibit T-cell proliferation via inhibitory effects on calcineurin (Fruman et al., 1992). Following SCI, treatment with CsA reduced T-cell infiltration into the CNS which occurred in parallel with a reduction in macrophage activation; this is possibly due to decreased T-cell cytokines in the injury site, although this was not specifically evaluated (Lu et al., 2010). Importantly, treatment with CsA improved outcomes whether given prophylactically or therapeutically, although earlier treatment seemed to provide greater benefit (Ibarra et al., 2003; McMahon et al., 2009).

Inhibition of T-cell function via antibody-mediated blockade of CD25, the high-affinity α chain of the interleukin (IL)-2 receptor, beginning at six weeks post-injury improved functional recovery in contused mice, suggesting that the inflammatory environment within the chronically injured spinal cord may have negative effects on any reparative processes that are initiated within the site (Arnold and Hagg, 2011). CD25 is expressed on recently activated CD4 + T effector cells and naturally occurring CD4 + regulatory T-cells (nTregs) which endows them with the ability to respond to IL-2 signaling, a requirement for subsequent antigen-specific proliferation and differentiation. Because CD25 is constitutively expressed by Tregs and is required for their survival and proliferation (Furtado et al., 2002; Littman and Rudensky, 2010), anti-CD25 treatment is generally considered to act via downregulation or inactivation of Tregs (Arnold and Hagg, 2011). However, it is also