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The paradox of chronic neuroinflammation, systemic immune suppression and autoimmunity after traumatic chronic spinal cord injury

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Abstract

During the transition from acute to chronic stages of recovery after spinal cord injury (SCI), there is an evolving state of immunologic dysfunction that exacerbates the problems associated with the more clinically obvious neurologic deficits. Since injury directly affects cells embedded within the “immune privileged/specialized” milieu of the spinal cord, maladaptive or inefficient responses are likely to occur. Collectively, these responses qualify as part of the continuum of “SCI disease” and are important therapeutic targets to improve neural repair and neurological outcome. Generic immune suppressive therapies have been largely unsuccessful, mostly because inflammation and immunity exert both beneficial (plasticity enhancing) and detrimental (e.g. glia- and neurodegenerative; secondary damage) effects and these functions change over time. Moreover, “compartmentalized” investigations, limited to only intraspinal inflammation and associated cellular or molecular changes in the spinal cord, neglect the reality that the structure and function of the CNS is influenced by systemic immune challenges and that the immune system is hardwired into the nervous system. Here, we consider this interplay during the progression from acute to chronic SCI. Specifically, we survey impaired/non-resolving intraspinal inflammation and the paradox of systemic inflammatory responses in the face of ongoing chronic immune suppression and autoimmunity. The concepts of *systemic inflammatory response syndrome* (SIRS),

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compensatory anti-inflammatory response syndrome (CARS) and ‘neurogenic’ spinal cord injury-induced immune depression syndrome (SCI-IDS) are discussed as determinants of impaired ‘host-defense’ and trauma-induced autoimmunity.

I. Introduction

Injury to the spinal cord elicits a robust intraspinal inflammatory response (Popovich et al., 1996; Schwab et al., 2001; Rice et al., 2005; Fleming et al., 2006). Consecutively, an immune modulatory response evolves in parallel including potent anti-inflammatory mechanisms both within and outside the spinal cord, presumably to regulate ongoing inflammation initiated by trauma (Lucin et al., 2007; 2009; Riegger et al., 2007; 2009, for review see Meisel et al., 2005; Irwin and Cole, 2011) (Fig. 1). Whether these are functionally effective inflammatory or anti-inflammatory reactions is questionable, especially since there is no evidence that either is resolved in affected individuals or animal models. Indeed, intraspinal inflammation persists indefinitely (Prüss et al., 2011; Popovich et al., 1997; Rosenberg et al., 2005) and depending on injury level, anti-inflammatory or even autoimmune pathologies develop (Popovich et al., 1997; Hayes et al., 2002; Ankeny 2006; Zajarias-Fainsod et al., 2012). Interactions between the central nervous and immune systems, i.e., the two main systems regulating homeostasis throughout the body, are not limited to aberrant immune cell activation/accumulation behind the blood-spinal cord barrier (BSB). Instead, SCI affects the entire immune system (Fig. 1).

Dynamic interactions between the “immune-privileged/-specialized” spinal cord and systemic immune organs innervated by the CNS are critical considerations for the evolution of the “SCI-disease” state that is initiated by traumatic SCI (Popovich and McTigue, 2009). In fact, even though the immune response is vital for maintenance of tissue homeostasis, immune system function continues to change as the injury evolves from the acute to the chronic state. The loss or dysfunction of vegetative innervation to lymphatic and endocrine tissues leads to a defective immune response long after the initial trauma (Meisel et al., 2005; Zhang et al., 2013). Here, we highlight different mechanisms that help explain protracted immune dysregulation including the development of chronic immune suppression and systemic autoimmunity. By doing so, we will address the localized immune response at the spinal cord lesion site and the impact on immune system function.

II. Intraspinal inflammation caused by trauma persists indefinitely

The inflammatory response elicited by trauma has long been viewed as an acute response, distinct from chronic inflammation. Nevertheless, intraspinal inflammation after SCI includes a non self-limiting, smoldering inflammatory cascade (Prüss et al., 2011; Rosenberg et al., 2005), that is conserved in different species including humans (Popovich et al., 1997; Fleming et al., 2006; Dulin et al., 2013; Blight, 1991; Kigerl et al., 2006).

Historically, immune system activation has been implicated in the pathogenesis of post-traumatic secondary injury, a delayed and progressive form of neurodegeneration that exacerbates cell death beyond the site of primary mechanical trauma (Dusart and Schwab, 1994; Fleming et al., 2006; Dulin et al., 2013; Blight, 1991; Popovich, 2000; Schwab et al.,

2006). The cellular and molecular inflammatory cascades induced by SCI include: activation and proliferation of resident microglia and astrocytes; infiltration of circulating innate immune cells including neutrophils, monocytes and lymphocytes; enhanced intraspinal synthesis and release of cytokines, chemokines and other vasoactive substances (e.g., histamine, complement proteins) by neuronal and non-neuronal cell types. The concomitant effects of triggering cell death with enhanced axonal sprouting or other indices of repair (e.g., progenitor cell proliferation/differentiation or revascularization), due to the simultaneous local release of neurotoxic and trophic factors by activated leukocytes, glia and neurons explains in part the paradoxical effects of intraspinal inflammation. The dichotomized perception of “good” and “bad” inflammation is overly simplistic and likely a reflection of our ignorance regarding the functional hierarchy and dynamics of neuro-immune interactions after SCI. Functional deciphering of distinct glia and leukocyte phenotypes and their relationship to changes in immunologic responsiveness throughout the body will offer a more precise understanding of the complexity of this multi-orchestrated response. More detail for each of the above components of intraspinal inflammation and the significance of these events are described throughout other reviews in this special issue and also in previous reviews (Ankeny et al., 2009; Donnelly and Popovich 2008; Popovich and Longbrake, 2008; Lucin and Wyss-Coray, 2009).

A key but poorly understood feature of intraspinal inflammation is the chronicity of this response (Prüss et al., 2011; Schwab et al., 2000). Chronic inflammation, also classified as “nonresolving inflammation”, implies that inflammation is normally controlled by active regulatory mechanisms (Nathan and Ding, 2010; Serhan and Savill, 2005). Failure to resolve inflammation results in aberrant tissue remodeling and organ dysfunction (Serhan and Savill, 2005; Serhan et al., 2007; Nathan and Ding, 2010). Consequently, effective repair and wound healing require coordinated inflammation with timely resolution (Serhan et al., 2007). Besides anti-inflammatory strategies, which aim to reduce leukocyte infiltration or survival at site of inflammation, naturally occurring resolution-promoting agonists, including resolvins E1 and protectin D1, exert similar effects (Schwab et al., 2007). Novel resolution phase promoting-agonists, such as the lipid-derived resolvins, protectins and maresins have been identified to exert potent stereoselective actions with human cells and animal disease models displaying features of incomplete resolution and are referred to as specialized pro-resolving mediators (SPM) and qualify as targets to treat neuropathology associated with a deficiency to resolve from inflammation (Serhan and Savill, 2005; Serhan et al., 2007).

There are no empirical data to show that inflammation resolves after experimental or human SCI. Conversely, an abundance of data indicate that inflammation persists indefinitely within the injury microenvironment. Although inflammatory cells persist at/nearby the injury site for months post-injury, none are as prominent as activated microglia and monocyte-derived macrophages, which persistently synthesize inflammatory enzymes that have been linked with chronic pathology and loss of function (Schwab et al., 2000; Dulin et al., 2013). The mechanisms underlying sustained inflammation are not known but several variables must be considered. For example, the oxidative lesion microenvironment may damage leukocyte (and glial) mitochondria, which could impair normal cellular functions including the ability to sustain self-repair or maintenance functions (Lin et al., 2007; Ohri et

al., 2011; Sullivan et al., 2005). Phagocytosis by microglia and macrophages is one example of a maintenance function gone awry that could exacerbate the chronicity of inflammation. Cellular and myelin debris are potent inflammatory signals that persist indefinitely at and nearby the injury site because of inefficient or impaired phagocytosis (Magnus et al., 2002; Vallieres et al., 2006; George and Griffin, 1994). A complementary explanation is that within an “immune privileged/-specialized” site like the spinal cord, the threshold of tissue damage caused by blunt trauma, compression or transection injury may exceed the capacity of normal resolution pathways to resolve inflammation (Prüss et al., 2011). This appears to be true even in patients with multiple sclerosis (MS), an inflammatory human CNS disease with comparatively less tissue damage (Prüss et al., 2013). A ‘neurogenic’ explanation for prolonged intraspinal inflammation is exemplified by the appearance of activated microglia, even in spinal regions remote from the injury site where intrinsic regulatory molecules expressed by neurons tonically regulate microglia. As a consequence of SCI and subsequent neurodegeneration, such control is lost and microglia become activated (Cardona et al., 2006; Meuth et al., 2008). Chronic remote activation of microglia has been implicated in the onset and progression of neuropathic pain (Schwab et al., 2005; Detloff et al., 2008; Hains and Waxman, 2006; Zhao et al., 2007). Lastly, metabolic changes could precipitate chronic inflammation. Just as obesity and associated metabolic syndromes contribute to atherosclerosis, another form of chronic inflammation (Nathan and Ding, 2010), a cardio-metabolic syndrome develops after SCI and could exacerbate neuroinflammation and neurologic dysfunction (Bigford et al., 2013; Gilbert et al., 2014).

Although protracted recruitment and activation of leukocytes and glia cannot be excluded as a mechanism to explain the “smoldering” chronic inflammatory response in traumatized spinal cord, a resolution deficit is also likely (Fig. 2). When objective, quantitative measures were applied to an experimental model of SCI, the persistence (“dwell time”) of different leukocyte subpopulations was revealed. Cell type-specific resolution intervals (time between maximum cell numbers and the point when they are reduced to 50%) vary from 1.2-1.5 days for neutrophils and T lymphocytes but are significantly increased to 15 or 55 days for B cells or microglia/macrophages, respectively. The absolute dwell time of leukocyte numbers exceeds the resolution interval as a resolution plateau may remain on supra-normal levels long after SCI. This holds in particular true for microglia/macropages and B-lymphocytes resulting in elevated resolution plateaus cell whereas T-lymphocyte and granulocytes get cleared in a much more effective manner from the lesion site (Prüss et al., 2011)(Fig. 2).

Residual activated microglia/macrophages are likely to undermine blood-spine-barrier closure after SCI thereby thwarting reconstitution of a critical feature of CNS immune privilege (Schwab at, 2000; Popovich et al., 1996b; Dulin et al., 2013). These distinct resolution intervals also suggest that a different repertoire of clearance receptors exists on these different leukocyte subpopulations. Thus, the aim of reducing dwell time of inflammatory cells at the CNS lesion or in peripheral tissues (see Anthony et al., this issue) is an alternative to the conventional anti-inflammatory strategies, which solely aim to reduce infiltrating leukocyte cell numbers at the lesion site (Prüss et al., 2011). Chronic inflammation is associated with impaired tissue remodeling (Serhan and Savill, 2005).

Indeed, there is no context in which chronic inflammation is beneficial. Instead, it is associated with excessive parenchyma destruction and *functio laesa* Serhan et al., 2007).

Impaired resolution of inflammation leads to an extended presentation of self-epitopes, which are usually shielded from overt immune attacks by a blood brain barrier (BBB). The immunologically silent, non-phlogistic clearance of apoptotic cells is crucial for maintaining tolerance to self-antigens (Uederhardt et al., 2012; Savill et al., 2002). Uncleared apoptotic cells eventually lose membrane integrity and release immunogenic self-antigens. This can elicit autoimmunity. The autoimmune pathogenesis of systemic lupus erythematosus (SLE), in humans and mouse models, has been attributed in parts to failed clearance of apoptotic cells (Munoz et al., 2010; Nagata et al., 2010). Likewise, the inefficient phagocytosis of apoptotic cells by macrophages can impair or delay resolution pathways and the exacerbated inflammation can trigger autoimmunity (Nathan and Ding, 2010). After SCI, autoimmunity against CNS antigens develops (see also Jones et al., this issue) and represents a putative target for minimizing chronic neuronal degeneration and aberrant connectivity. Even though trauma and subsequent injury to the blood-spinal cord barrier (BSB) can be linked to neurologic relapses in Multiple Sclerosis (MS) patients and exacerbated pathology and loss of function in predisposed rodent models (Poser et al., 1994; Jones et al., 2002), this *de novo* autoimmunity elicited by SCI, i.e., trauma-induced autoimmunity, needs to be distinguished from the defined disease entity of MS, which is characterized by distinct diagnostic criteria with a different etiology. Nevertheless there are also overlapping disease mechanisms.

The non-resolving inflammation that occurs after SCI recapitulates relevant neuropathological aspects of the primary progressive form of MS (PPMS). In both SCI and MS, chronically activated microglia/macrophages are associated with ongoing neurodegeneration. Such a compartmentalized inflammatory reaction in the spinal cord may drive chronic progression of neurodegeneration and demyelination (Lassmann et al., 2007). In the progressive phase of MS, new demyelinating lesions are rare but diffuse atrophy of the gray and white matter and changes in the macroscopically “normal-appearing white matter” (NAWM) become prominent (Lassmann et al., 2007; Rise et al., 2013). Likewise, in human SCI, a greater magnitude of progressive atrophy in exofocal gray and white matter over a period of ~1 year correlates with significantly impaired neurological function (Freund et al., 2013).

III. ‘Crosstalk’/interactions between the nervous and immune systems, and neurogenic regulation of immune system

Functional cross-talk between the nervous and immune systems is achieved by the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Elenkov, et al., 2000). The ANS is comprised of the sympathetic nervous system (SNS) and the parasympathetic nervous system. These different arms of the ANS counter-regulate each other to control involuntary functions (e.g., heartbeat, digestion, secretion). A convincing body of evidence shows that primary and secondary lymphoid tissues are innervated by the SNS and cells of the immune system bear specific surface receptors for neurotransmitters, hormones and neuropeptides associated with the SNS and HPA axis (Meisel et al., 2005). Similarly, through the release of cytokines and/or chemokines during an active immune

response, leukocytes communicate with and regulate CNS function. Cytokine and chemokine receptors are expressed on peripheral sensory nerves and can access cells in brain and spinal cord via specific transport mechanisms or the circumventricular organs (sites where blood-brain barrier is “leaky”). Cytokines are known to affect the survival and function of neurons and glia and can activate both the SNS and the HPA axis through a complex corticotropin-releasing hormone (CRH)-dependent pathway (long feedback loop between the immune system and the brain (hypothalamus) (Meisel et al., 2005).

SIRS and CARS

As a model for understanding the seemingly conflicting dynamics of acute and chronic intraspinal inflammation with delayed systemic immune suppression (see SCI-IDS below), it is useful to consider the pathophysiology of sepsis. Sepsis elicits a systemic inflammatory response syndrome (SIRS) and a compensatory anti-inflammatory response syndrome (CARS). In response to injury or infection, SIRS develops but in parallel CARS is triggered to terminate inflammation (Hotchkiss et al., 2013a,b). A balance in both the intensity and duration of these responses is needed to restore homeostasis within affected tissues throughout the body; an imbalance or overly exuberant response of either SIRS or CARS causes excess inflammation or chronic immune dysfunction, respectively. Neither result is ideal and alone or unregulated, each syndrome can have pathological effects. The dogma that sepsis is the result of an overzealous inflammatory reaction has caused most research and clinical therapies directed toward that disease to focus on limiting inflammation, although with the recent attention focused on the pathologic potential of CARS, therapies to enhance inflammation have started to emerge (Hotchkiss et al., 2013a,b).

Although distinct from sepsis, “sterile” inflammatory lesions in the CNS (e.g., SCI or brain injury) trigger a host response resembling SIRS (see Anthony and Couch, this issue). Autoregulatory mechanisms akin to CARS also develop; however, loss of vegetative input (i.e., SNS) to lymphoid and endocrine organs is unique to SCI and culminates in a condition referred to as spinal cord injury-induced immune depression syndrome (SCI-IDS) (Meisel et al., 2005; Riegger et al., 2007; 2009).

SCI-IDS and infection

SCI effectively ablates normal preganglionic innervation by the SNS to immune organs. This “neurogenic immune ablation” damages the normally well-balanced interplay between the immune system and the CNS culminating in the onset of SCI-IDS. SCI-IDS develops quickly, within 24h, affects cells of both the innate and adaptive immune systems, is independent of the iatrogenic application of high dose corticosteroids and is analogously represented in animal and human SCI justifying its translational relevance and extends into the chronic phase after SCI (Campagnolo et al., 1997; Furlan et al., 2006; Lucin et al., 2007; 2009; Riegger et al., 2007; 2009; Zhang et al., 2013). Similar complications of immunosuppression occur after traumatic brain injury and cerebral infarction (stroke) and are referred to as CNS injury-induced immune deficiency syndrome (CIDS) (Meisel, et al., 2005). Rapid-onset SCI-IDS may develop as a means to confine or prevent pathologic autoimmunity against self-antigens that are liberated or newly expressed by SCI. Conversely, autoimmunity might result from insufficient or weak induction of SCI-IDS

(„SCI-IDS-escape“), perhaps due to SCI at a lower spinal level or a less severe injury with spared neuro-immune communication (Figs. 1 & 4). SCI-IDS might also decrease the efficacy of protective immunizations (see below; also see Jones et al., this issue).

Previous reports from us and others indicate that post-SCI immune suppression during both the acute and chronic phases is level-dependent (T3 SCI but not T9 SCI) and is caused in part by dysregulation of the SNS and HPA axis, which results from the loss of descending modulation of spinal sympathetic pre-ganglionic neurons (SPNs) lying caudal to the lesion, as well as the exaggerated spinal circuitry/autonomic reflex triggered by a strong sensory input (Cruse, et al., 1996, Cruse, et al., 1993, Lucin, et al., 2007, Lucin, et al., 2009, Zhang, et al., 2013). Moreover, lesion-height dependent atrophy/involution of secondary lymphatic organs has been described (Lucin et al., 2007; Brommer et al., unpublished data).

SPNs are the source of all sympathetic outflow from the thoracic spinal cord (T3-T13) (Elenkov, et al., 2000). Activation of SPNs causes release of norepinephrine (NE) and GCs from post-ganglionic nerve terminals and the adrenal gland (Engeland and Arnhold, 2005). Visceral and somatic afferents activate SPNs, which send cholinergic projections to post-ganglionic neurons that innervate target organs including blood vessels, lymphoid tissues (e.g., spleen) and the adrenal medulla. SPNs also directly innervate the adrenal cortex providing a rapid and direct mechanism for enhancing GC release (Engeland and Arnhold, 2005). Physiological concentrations of GCs and NE ensure normal immune function but recurrent or prolonged activation of glucocorticoid receptors (GRs) or beta-2 adrenergic receptors (β 2AR) is immunosuppressive (Nance and Sanders, 2007). Thus, sustained or uncontrolled activation of the SNS causes aberrant accumulation of NE and GCs in the circulation and immune organs and could promote immune suppression.

A decentralized SNS is also involved in the occurrence of autonomic dysreflexia (AD), which was recently identified as a cause/mechanism of secondary immune deficiency after SCI (Zhang, et al., 2013). Autonomic dysreflexia is triggered by diverse stimuli, including distension of bladder or colon, which cause reflex activation of SPNs and exaggerated discharge of sympathetic neurons. As a result, blood pressure rises to exceedingly high levels. In parallel, the increased firing of noradrenergic fibers innervating lymphoid tissues and the adrenal cortex trigger NE and GC release, respectively. Because the pressor response associated with autonomic dysreflexia can cause significant physical and psychological stress, the HPA axis is stimulated in parallel causing a vicious cycle leading to additional GC release.

Most immune cells express adrenergic and GC receptors. β 2AR is the predominant type of adrenergic receptor expressed on B and T lymphocytes in the spleen. NE spike causes lethal overstimulation of β 2AR on splenic lymphocytes, and circulating GCs synergize with NE to induce apoptotic signaling in these cells (Lucin, et al., 2007, Lucin, et al., 2009). Secondary lymphoid organs (e.g., spleen) are heavily innervated by sympathetic nerve fibers. Aberrant accumulation of CAs and GCs is associated with the global loss of B and T cells and leucopenia in these immune organs, sites where B cells interact with T cells and APCs to mount immune responses against pathogens and where antibodies are produced (Lucin, et al., 2007). Thus, the occurrence of episodic autonomic dysreflexia causes considerable

systemic stress culminating in excess release of circulating GCs and intra-splenic NE, which aggravates lymphocyte depletion and corresponding impairments of immune response and antibody production, and finally chronic immune suppression (Zhang, et al., 2013).

Clinically relevant yet widely underappreciated; acute and chronic SCI-IDS also increases susceptibility to infection (Brommer et al., unpublished data). Infection is the leading cause of morbidity and mortality in patients with SCI (DeVivo et al., 1989; Soden et al., 2000). Infectious complications or diseases are prevalent (>50%) and often occur secondary to SCI, and increase in incidence in quadriplegics and high-level paraplegics leading to a mortality rate of ~4-17% (Failli, et al., 2012). Recent large neuroepidemiological studies with more than 1400 enrolled patients demonstrate that post-SCI infections are independent risk factors for significantly poorer neurological recovery (Failli, et al., 2012; Meisel, et al., 2005). Thus, infections qualify as independent neurobiological rehabilitation confounders that impair the endogenous recovery potential after SCI (Failli et al., 2012; Dietz and Fouad, 2013).

The underlying neurobiology of impaired neurological recovery is under investigation. Among others, exacerbated neurodegeneration (Cunningham et al., 2005) and axonal injury (Moreno et al., 2001) but also ‘sickness behavior’ (Teeling et al., 2010) were reported after systemic endotoxin challenge as a model of systemic infections (Perry, 2003). From a teleological view SCI-IDS could be understood as a conserved mechanism to prevent the development of autoimmunity against CNS specific epitopes, which become assessable by the innate and adaptive immune arm after SCI due to a defective BSB (Fig. 4). We hypothesize that in patients with a low SCI-IDS penetrance a higher risk for robust CNS-autoimmunity will be observed (Schwab et al., 2006). The pathoimmunological link between severity of SCI-IDS and developing autoimmunity will be investigated by the ‘SCIentinel Trail’ recruiting at present (Kopp et al., 2013).

IV. Autoimmune responses after SCI

Emerging clinical and experimental data indicate that SCI elicits systemic autoimmunity (Table 1). Autoimmunity develops when cells of the immune system recognize and mount an immune response against “self” antigens which include proteins, carbohydrates, lipids and nucleic acids that are normally found throughout the body. Autoimmunity can be viewed as a continuum of autoinflammatory (self-directed tissue inflammation dominated by innate immune system) and autoimmune reactions (loss of immunological tolerance with activation of self-directed adaptive immune responses) reactions (McGonagle and McDermott, 2006). The former involves the coordinated activation of inflammasomes and uncontrolled cytokine synthesis with robust activation of myeloid cells (e.g., neutrophils, monocytes/macrophages; also see Kigerl et al., this issue) and the latter activation of self-reactive lymphocytes and enhanced synthesis of autoantibodies (Hayes et al., 2002; Davies et al., 2007; also see Jones, this issue). Each has been implicated in progression of secondary injury after SCI (Ankeny and Popovich, 2010; Zhang and Popovich, 2011). The combination of primary and secondary injury after SCI causes extensive tissue damage to the spinal cord and blood-spinal cord barrier. Subsequently, CNS self-antigens (e.g., myelin, phospholipids, structural proteins) are released into the circulation and drain into secondary lymphoid organs where neuroantigen specific T and B lymphocytes become activated with a

subpopulation of lymphocytes acquiring the ability to cross the intact blood-spinal cord barrier to form infiltrating clusters in Virchow-Robin spaces. These perivascular cell accumulations resemble those seen in the EAE model of MS (Popovich et al., 1996a) (Fig. 3a). Clinical signs of disease, such as flaccid tail paralysis, also were observed in naïve animals receiving lymphocytes from littermates suffering acute SCI (Popovich et al., 1996a). Despite the encephalitogenic potential of SCI-activated lymphocytes, protective T cells also are activated after SCI and a subset of endogenous autoreactive cells may exert 'repairing' effects on the injured CNS (Schwartz and Kipnis, 2005; also see Jones, this issue).

In classical CNS inflammatory diseases (e.g., MS), ectopic lymphoid-like follicles form adjacent to large intraparenchymal inflammatory lesions (Aloisi et al., 2007). Activated B and T cells also infiltrate and accumulate within the traumatically injured spinal cord where they form large cellular clusters that are reminiscent of germinal centers with follicles that are normally found in spleen and lymph nodes (Ankeny, et al., 2006; 2009) (Fig. 3b). The pathogenic significance of these clusters is not clear; however, if they are functionally analogous to those that form in MS, they may contribute to chronic gray and white matter pathology. Recent data show that in cases of MS, ectopic CNS B-cell follicles co-localized with a corresponding gradient of neuronal loss (Magliozzi et al., 2010).

Activated B and T cells secrete inflammatory cytokines and other co-stimulatory factors. Moreover, the formation of antibody-antigen complexes causes tissue damage through recruitment and activation of complement and Fc receptor-bearing cells (e.g. macrophages). In SCI mice, antibody and complement 1q (C1q) decorate neuronal somata in spared tissue and co-localize with regions of axonal injury and demyelination (Ankeny, et al., 2009). Also, axon loss, demyelination and inflammatory cell accumulation are reduced and functional recovery is improved in SCI mice that are deficient in complement C3 (Qiao, et al., 2006). When injected into intact spinal cord, antibodies purified from SCI mice cause pathology and neurological dysfunction; however, the destructive effects of SCI autoantibodies are attenuated when injected into mice deficient in complement C3 or Fc receptor γ chain (Ankeny, et al., 2009). Together, these data provide a basis for a deeper understanding why recovery from SCI is improved and neuropathology is reduced in mice lacking B cells (Ankeny, et al., 2009). SCI also triggers autoimmune T and B cell responses in humans but the pathogenic significance of these responses remains uncertain (Kil et al., 1999; Saltzman et al., 2013). Autoimmunity after SCI is considered a dynamic process, which is likely to be a function of the extent of SCI-IDS (Meisel et al., 2005; Kopp et al., 2013) and consecutive infections (Enouz et al. 2012) supported by clinical observations demonstrating elevated auto-antibody titers in patients with concomitant infections (Davis et al., 2007) (Fig. 4).

V. Possible reversal of immune dysregulation induced by SCI

Drugs exist that could be used to overcome immune dysfunction or trauma-induced autoimmunity after SCI. The onset of immunosuppression after SCI is primarily caused by unregulated activation of SPNs, which causes aberrant accumulation of NE and GCs, leading to prolonged activation of adrenergic receptors (e.g., β 2ARs) and GRs expressed on immune cells. In mice, selective β 2AR (butoxamine) and GR antagonists (RU486) can

significantly reduce leukocyte killing and restore immune function after both acute and chronic high-level SCI (Lucin, et al., 2007, Zhang, et al., 2013). Other regimens of adrenoceptor blockade have proven to be similarly effective in potentiating immune responses after stroke and could represent therapeutic targets for reversing CIDS (Ajmo, et al., 2009, Prass, et al., 2003). In addition, since autonomic dysreflexia was recently detected as an underlying mechanism of immune suppression after SCI, any strategy that can prevent AD should also alleviate SCI-IDS and consequently, reduce mortality and improve neurological outcome. For example, gabapentin, a GABA (Gamma-Aminobutyric acid) analogue used clinically to treat neuropathic pain, has also been shown in experimental models to significantly reduce tail spasticity and autonomic dysreflexia after severe SCI (Rabchevsky, et al., 2012).

Most experimental data indicate that SCI autoantibodies can cause tissue damage; therefore, strategies to remove or deplete autoantibodies or suppress B cell activation could be neuroprotective (Martin and Chan, 2006). Although some B cell depleting monoclonal antibodies (e.g., Rituxan®, Ocrelizumab®) fusion proteins or biologicals that regulate B-cell survival factors (e.g., BAFF and APRIL) have or are being tested as therapies for classical forms of autoimmune disease (Mackay, et al., 2003), similar strategies have not been tested in stroke, CNS injury or neurodegenerative disease.

The detection and identification of autoantibodies also could have diagnostic and therapeutic value for SCI. The presence of specific antibodies in patients offers an opportunity for early diagnosis of immune dysfunction after SCI. In the future, it may be possible to stratify the severity of injuries in SCI populations based on the magnitude or specificity of autoantibody profiles. Such an approach could be useful for predicting responders and non-responders for clinical trial design and perhaps for devising uniquely tailored immune-modulatory treatments. Indeed, a preponderance of autoantibodies of a specific isotype or antigen specificity may help predict changes in specific neurological functions and/or systemic pathologies.

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Abbreviations

AD	Autonomic dysreflexia
AIS	ASIA impairment scale
ANS	Autonomous nervous system
ASIA-score	American Spinal Injury Association (has been revised and referred to as INSCSCI = International Standards for neurological classification of spinal cord injury)

BSB	Blood spinal cord barrier
BDNF	Brain derived neurotrophic factor
CARS	counter regulatory anti-inflammatory syndrome
CIDS	CNS injury-induced immune depression syndrome
GCs	Glucocorticoids
HPA-axis	Hypothalamus-Pituitary-Adrenal axis
IVIG	Intravenous immunoglobulins
NE	Norepinephrine
NT-3	Neurotrophin-3
SCI-IDS	Spinal cord injury-induced immune depression syndrome
SIRS	Systemic inflammatory response syndrome
SNS	Sympathetic nervous system
SPN	Sympathetic pre-ganglionic neuron

References

1. Ajmo CT Jr, Collier LA, Leonardo CC, Hall AA, Green SM, Womble TA, Cuevas J, Willing AE, Pennypacker KR. Blockade of adrenoreceptors inhibits the splenic response to stroke. *Exp Neurol*. 2009; 218:47–55. [PubMed: 19371742]
2. Aloisi F. Immune function of microglia. *Glia*. 2001; 36:165–179. [PubMed: 11596125]
3. Ankeny DP, Guan Z, Popovich PG. B cells produce pathogenic antibodies and impair recovery after spinal cord injury in mice. *J Clin Invest*. 2009; 119:2990–2999. [PubMed: 19770513]
4. Ankeny DP, Lucin KM, Sanders VM, McGaughy VM, Popovich PG. Spinal cord injury triggers systemic autoimmunity: evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis. *J Neurochem*. 2006; 99:1073–1087. [PubMed: 17081140]
5. Ankeny DP, Popovich PG. Mechanisms and implications of adaptive immune responses after traumatic spinal cord injury. *Neuroscience*. 2009; 158:1112–1121. [PubMed: 18674593]
6. Ankeny DP, Popovich PG. B cells and autoantibodies: complex roles in CNS injury. *Trends Immunol*. 2010; 31:332–338. [PubMed: 20691635]
7. Anthony DC. CNS injury affects on systemic inflammation. *Exp Neurol*. 2014 this issue.
8. Beck KD, Nguyen HX, Galvan MD, Salazar DL, Woodruff TM, Anderson AJ. Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment. *Brain*. 2010; 133:433–47. [PubMed: 20085927]
9. Beers DR, Henkel JS, Zhao W, Wang J, Huang A, Wen S, Liao B, Appel SH. Endogenous regulatory T lymphocytes ameliorate amyotrophic lateral sclerosis in mice and correlate with disease progression in patients with amyotrophic lateral sclerosis. *Brain*. May; 2011 134(Pt 5): 1293–314. [PubMed: 21596768]
10. Bigford GE, Bracchi-Ricard VC, Nash MS, Bethea JR. Alterations in mouse hypothalamic adipokine gene expression and leptin signaling following chronic spinal cord injury and with advanced age. *PLoS One*. 2012; 7:e41073. [PubMed: 22815920]
11. Bigford GE, Bracchi-Ricard VC, Keane RW, Nash MS, Bethea JR. Neuroendocrine and cardiac metabolic dysfunction and NLRP3 inflammasome activation in adipose tissue and pancreas following chronic spinal cord injury in the mouse. *ASN Neuro*. 2013; 5:243–55. [PubMed: 23924318]

12. Blight AR. Morphometric analysis of a model of spinal cord injury in guinea pigs, with behavioral evidence of delayed secondary pathology. *J Neurol Sci.* 1991; 103:156–71. [PubMed: 1880533]
13. Bradl M, Bauer J, Flügel A, Wekerle H, Lassmann H. Complementary contribution of CD4 and CD8 T lymphocytes to T-cell infiltration of the intact and the degenerative spinal cord. *Am J Pathol.* May. 2005; 166(5):1441–50. [PubMed: 15855644]
14. Brommer B, Engel E, Kopp MA, Watzlawick R, Müller S, Failli V, Chen YY, DeVivo MJ, Dirnagl U, Meisel A, Schwab JM. Spinal Cord Injury increases the susceptibility for bacterial infection in a lesion height dependent manner – evidence for a neurogenic immune ablation ('immune paralysis'). In preparation. 2014
15. Campagnolo DI, Bartlett JA, Keller SE, Sanchez W, Oza R. Impaired phagocytosis of *Staphylococcus aureus* in complete tetraplegics. *Am J Phys Med Rehabil.* 1997; 76:276–280. [PubMed: 9267186]
16. Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G, Dombrowski S, Dutta R, Lee JC, Cook DN, Jung S, Lira SA, Littman DR, Ransohoff RM. Control of microglial neurotoxicity by the fractalkine receptor. *Nat Neurosci.* 2006; 9:917–24. [PubMed: 16732273]
17. Cruse JM, Keith JC, Bryant ML Jr, Lewis RE Jr. Immune system-neuroendocrine dysregulation in spinal cord injury. *Immunol Res.* 1996; 15:306–314. [PubMed: 8988397]
18. Cruse JM, Lewis RE Jr, Bishop GR, Kliesch WF, Gaitan E, Britt R. Decreased immune reactivity and neuroendocrine alterations related to chronic stress in spinal cord injury and stroke patients. *Pathobiology.* 1993; 61:183–192. [PubMed: 8216840]
19. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci.* 2005; 25:9275–84. [PubMed: 16207887]
20. Davies AL, Hayes KC, Dekaban GA. Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Arch Phys Med Rehabil.* 2007; 88:1384–93. [PubMed: 17964877]
21. DeVivo MJ, Kartus PL, Stover SL, Rutt RD, Fine PR. Cause of death for patients with spinal cord injuries. *Arch Intern Med.* 1989; 149:1761–1766. [PubMed: 2669663]
22. Detloff MR, Fisher LC, McGaughy V, Longbrake EE, Popovich PG, Basso DM. Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats. *Exp Neurol.* 2008; 212:337–47. [PubMed: 18511041]
23. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. *Brain* ahead of print. 2013
24. Donnelly DJ, Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. *Exp Neurol.* 2008; 209:378–388. [PubMed: 17662717]
25. Dusart I, Schwab ME. Secondary cell death and the inflammatory reaction after dorsal hemisection of the rat spinal cord. *Eur J Neurosci.* 1994; 6:712–24. [PubMed: 8075816]
26. Dulin JN, Karoly ED, Wang Y, Strobel HW, Grill RJ. Licofelone modulates neuroinflammation and attenuates mechanical hypersensitivity in the chronic phase of spinal cord injury. *J Neurosci.* 2013; 33:652–64. [PubMed: 23303944]
27. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev.* 2000; 52:595–638. [PubMed: 11121511]
28. Engeland WC, Arnhold MM. Neural circuitry in the regulation of adrenal corticosterone rhythmicity. *Endocrine.* 2005; 28:325–332. [PubMed: 16388123]
29. Enouz S, Carrié L, Merkler D, Bevan MJ, Zehn D. Autoreactive T cells bypass negative selection and respond to self-antigen stimulation during infection. *J Exp Med.* 2012; 209:1769–79. [PubMed: 22987800]
30. Failli V, Kopp MA, Gericke C, Martus P, Klingbeil S, Brommer B, Laginha I, Chen Y, DeVivo MJ, Dirnagl U, Schwab JM. Functional neurological recovery after spinal cord injury is impaired in patients with infections. *Brain.* 2012; 135:3238–3250. [PubMed: 23100450]

31. Fleming JC, Norenberg MD, Ramsay DA, Dekaban GA, Marcillo AE, Saenz AD, Pasquale-Styles M, Dietrich WD, Weaver LC. The cellular inflammatory response in human spinal cords after injury. *Brain*. 2006; 129:3249–69. [PubMed: 17071951]
32. Furlan JC, Krassioukov AV, Fehlings MG. Hematologic abnormalities within the first week after acute isolated traumatic cervical spinal cord injury: a case-control cohort study. *Spine (Phila Pa 1976)*. Nov 1; 2006 31(23):2674–83. [PubMed: 17077735]
33. Freund P, Weiskopf N, Ashburner J, Wolf K, Sutter R, Altmann DR, Friston K, Thompson A, Curt A. MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. *Lancet Neurol*. 2013; 12:873–81. [PubMed: 23827394]
34. George R, Griffin JW. Delayed macrophage responses and myelin clearance during Wallerian degeneration in the central nervous system: the dorsal radiculotomy model. *Exp Neurol*. 1994; 129:225–36. [PubMed: 7957737]
35. Gilbert O, Croffoot JR, Taylor AJ, Nash M, Schomer K, Groah S. Serum lipid concentrations among persons with spinal cord injury - A systematic review and meta-analysis of the literature. *Atherosclerosis*. 2014; 232:305–12. [PubMed: 24468143]
36. Gold R, Stangel M, Dalakas MC. Drug Insight: the use of intravenous immunoglobulin in neurology--therapeutic considerations and practical issues. *Nat Clin Pract Neurol*. 2007; 3:36–44. [PubMed: 17205073]
37. Hains BC, Waxman SG. Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. *J Neurosci*. 2006; 26:4308–17. [PubMed: 16624951]
38. Hayes KC, Hull TC, Delaney GA, Potter PJ, Sequeira KA, Campbell K, Popovich PG. Elevated serum titers of proinflammatory cytokines and CNS autoantibodies in patients with chronic spinal cord injury. *J Neurotrauma*. Jun. 2002; 19(6):753–61. [PubMed: 12165135]
39. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis*. 2013a; 3:260–8. [PubMed: 23427891]
40. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013b; 13:862–74. [PubMed: 24232462]
41. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol*. 2011; 11:625–32. [PubMed: 21818124]
42. Jones TB. Lymphocytes and autoimmunity after SCI. *Exp Neurol*. 2014 this issue.
43. Jones TB, Hart RP, Popovich PG. Molecular control of physiological and pathological T-cell recruitment after mouse spinal cord injury. *J Neurosci*. 2005; 25:6576–6583. [PubMed: 16014718]
44. Jones TB, Basso DM, Sodhi A, Pan JZ, Hart RP, MacCallum RC, Lee S, Whitacre CC, Popovich PG. Pathological CNS autoimmune disease triggered by traumatic spinal cord injury: implications for autoimmune vaccine therapy. *J Neurosci*. 2002; 22:2690–700. [PubMed: 11923434]
45. Kigerl KA, McGaughy VM, Popovich PG. Comparative analysis of lesion development and intraspinal inflammation in four strains of mice following spinal contusion injury. *J Comp Neurol*. 2006; 494:578–594. [PubMed: 16374800]
46. Kil K, Zang YC, Yang D, Markowski J, Fuoco GS, Vendetti GC, Rivera VM, Zhang JZ. T cell responses to myelin basic protein in patients with spinal cord injury and multiple sclerosis. *J Neuroimmunol*. 1999; 98:201–7. [PubMed: 10430053]
47. Kopp MA, Druschel C, Meisel C, Liebscher T, Prilipp E, Watzlawick R, Cinelli P, Niedeggen A, Schaser KD, Wanner GA, Curt A, Lindemann G, Nugaeva N, Fehlings MG, Vajkoczy P, Cabraja M, Dengler J, Ertel W, Ekkernkamp A, Martus P, Volk HD, Unterwalder N, Kölsch U, Brommer B, Hellmann RC, Ossami Saidy RR, Laginha I, Prüss H, Failli V, Dirnagl U, Schwab JM. The SCIntinel study - prospective multicenter study to define the spinal cord injury-induced immune depression syndrome (SCI-IDS) - study protocol and interim feasibility data. *BMC Neurol*. 2013; 13:168. [PubMed: 24206943]
48. Lassmann H, Brück W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol*. 2007; 17:210–8. [PubMed: 17388952]
49. Lin Y, Vreman HJ, Wong RJ, Tjoa T, Yamauchi T, Noble-Haeusslein LJ. Heme oxygenase-1 stabilizes the blood-spinal cord barrier and limits oxidative stress and white matter damage in the acutely injured murine spinal cord. *J Cereb Blood Flow Metab*. 2007; 27:1010–21. [PubMed: 17047682]

50. Lucin KM, Wyss-Coray T. Immune activation in brain aging and neurodegeneration: too much or too little? *Neuron*. 2009; 64:110–22. [PubMed: 19840553]
51. Lucin KM, Sanders VM, Popovich PG. Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. *J Neurochem*. 2009; 110:1409–1421. [PubMed: 19545280]
52. Lucin KM, Sanders VM, Jones TB, Malarkey WB, Popovich PG. Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. *Exp Neurol*. 2007; 207:75–84. [PubMed: 17597612]
53. Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. *Annu Rev Immunol*. 2003; 21:231–264. [PubMed: 12427767]
54. Magliozzi R, Howell OW, Reeves C, Roncaroli F, Nicholas R, Serafini B, Aloisi F, Reynolds R. A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. *Ann Neurol*. 2010; 68:477–93. [PubMed: 20976767]
55. Magnus T, Chan A, Savill J, Toyka KV, Gold R. Phagocytotic removal of apoptotic, inflammatory lymphocytes in the central nervous system by microglia and its functional implications. *J Neuroimmunol*. 2002; 130:1–9. [PubMed: 12225883]
56. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. *Annu Rev Immunol*. 2006; 24:467–496. [PubMed: 16551256]
57. Matsushita T, Horikawa M, Iwata Y, Tedder TF. Regulatory B cells (B10 cells) and regulatory T cells have independent roles in controlling experimental autoimmune encephalomyelitis initiation and late-phase immunopathogenesis. *J Immunol*. 2010; 185:2240–52. [PubMed: 20624940]
58. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med*. 2006; 3:e297. [PubMed: 16942393]
59. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci*. 2005; 6:775–786. [PubMed: 16163382]
60. Meuth SG, Simon OJ, Grimm A, Melzer N, Herrmann AM, Spitzer P, Landgraf P, Wiendl H. CNS inflammation and neuronal degeneration is aggravated by impaired CD200-CD200R-mediated macrophage silencing. *J Neuroimmunol*. 2008; 194:62–9. [PubMed: 18164423]
61. Mizrahi Y, Ohry A, Aviel A, Rozin R, Brooks ME, Schwartz M. Systemic humoral factors participating in the course of spinal cord injury. *Paraplegia*. 1983; 21:287–93. [PubMed: 6196708]
62. Moreno B, Jukes JP, Vergara-Irigaray N, Errea O, Villoslada P, Perry VH, Newman TA. Systemic inflammation induces axon injury during brain inflammation. *Ann. Neurol*. 2011; 70:932–42. [PubMed: 22190366]
63. Muñoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M. The role of defective clearance of apoptotic cells in systemic autoimmunity. *Nat Rev Rheumatol*. 2010; 6:280–9. [PubMed: 20431553]
64. Nagata S, Hanayama R, Kawane K. Autoimmunity and the clearance of dead cells. *Cell*. 2010; 140:619–30. [PubMed: 20211132]
65. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987–2007). *Brain Behav Immun*. 2007; 21:736–745. [PubMed: 17467231]
66. Nathan C, Ding A. Nonresolving inflammation. *Cell*. 2010; 140:871–82. [PubMed: 20303877]
67. Nguyen DH, Cho N, Satkunendrarajah K, Austin JW, Wang J, Fehlings MG. Immunoglobulin G (IgG) attenuates neuroinflammation and improves neurobehavioral recovery after cervical spinal cord injury. *J Neuroinflammation*. 2012; 9:224. [PubMed: 22998664]
68. Perry VH, Newman TA, Cunningham C. The impact of systemic infection on the progression of neurodegenerative disease. *Nat Rev Neurosci*. 2003; 4:103–12. [PubMed: 12563281]
69. Popovich PG, Stokes BT, Whitacre CC. Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. *J Neurosci Res*. 1996a; 45:349–63. [PubMed: 8872895]
70. Popovich PG, Horner PJ, Mullin BB, Stokes BT. A quantitative spatial analysis of the blood-spinal cord barrier. I. Permeability changes after experimental spinal contusion injury. *Exp Neurol*. 1996b; 142:258–75. [PubMed: 8934558]
71. Popovich PG, Wei P, Stokes BT. Cellular inflammatory response after spinal cord injury in Sprague-Dawley and Lewis rats. *J Comp Neurol*. 1997; 377:443–64. [PubMed: 8989657]

72. Popovich PG. Immunological regulation of neuronal degeneration and regeneration in the injured spinal cord. *Prog Brain Res.* 2000; 128:43–58. [PubMed: 11105668]
73. Popovich P, McTigue D. Damage control in the nervous system: beware the immune system in spinal cord injury. *Nat Med.* 2009; 15:736–7. [PubMed: 19584863]
74. Poser CM. The role of trauma in the pathogenesis of multiple sclerosis: a review. *Clin Neurol Neurosurg.* 1994; 96:103–10. [PubMed: 7924071]
75. Prass K, Meisel C, Hoflich C, Braun J, Halle E, Wolf T, Ruscher K, Victorov IV, Priller J, Dirnagl U, Volk HD, Meisel A. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J Exp Med.* 2003; 198:725–736. [PubMed: 12939340]
76. Prüss H, Rosche B, Sullivan AB, Brommer B, Wengert O, Gronert K, Schwab JM. Proresolution lipid mediators in multiple sclerosis -differential, disease severity-dependent synthesis - a clinical pilot trial. *PLoS One.* 2013; 8:e55859. [PubMed: 23409068]
77. Prüss H, Kopp MA, Brommer B, Gatzemeier N, Laginha I, Dirnagl U, Schwab JM. Non-resolving aspects of acute inflammation after spinal cord injury (SCI): indices and resolution plateau. *Brain Pathol.* 2011; 21:652–60. [PubMed: 21418368]
78. Qiao F, Atkinson C, Song H, Pannu R, Singh I, Tomlinson S. Complement plays an important role in spinal cord injury and represents a therapeutic target for improving recovery following trauma. *Am J Pathol.* 2006; 169:1039–1047. [PubMed: 16936276]
79. Rabchevsky AG, Patel SP, Lyttle TS, Eldahan KC, O'Dell CR, Zhang Y, Popovich PG, Kitzman PH, Donohue KD. Effects of gabapentin on muscle spasticity and both induced as well as spontaneous autonomic dysreflexia after complete spinal cord injury. *Front Physiol.* 2012; 3:329. [PubMed: 22934077]
80. Rice CM, Cottrell D, Wilkins A, Scolding NJ. Primary progressive multiple sclerosis: progress and challenges. *J Neurol Neurosurg Psychiatry.* 2013; 84:1100–6. [PubMed: 23418213]
81. Rice T, Larsen J, Rivest S, Yong VW. Characterization of the early neuroinflammation after spinal cord injury in mice. *J Neuropathol Exp Neurol.* 2007; 66:184–195. [PubMed: 17356380]
82. Riegger T, Conrad S, Schluesener HJ, Kaps HP, Badke A, Baron C, Gerstein J, Dietz K, Abdizahdeh M, Schwab JM. Immune depression syndrome following human spinal cord injury (SCI): a pilot study. *Neuroscience.* 2009; 158:1194–9. [PubMed: 18790013]
83. Riegger T, Conrad S, Liu K, Schluesener HJ, Adibzahdeh M, Schwab JM. Spinal cord injury-induced immune depression syndrome (SCI-IDS). *Eur J Neurosci.* 2007; 25:1743–7. [PubMed: 17432962]
84. Rosenberg LJ, Zai LJ, Wrathall JR. Chronic alterations in the cellular composition of spinal cord white matter following contusion injury. *Glia.* 2005; 49:107–20. [PubMed: 15390101]
85. Saltzman JW, Battaglino RA, Salles L, Jha P, Sudhakar S, Garshick E, Stott HL, Zafonte R, Morse LR. B-cell maturation antigen, a proliferation-inducing ligand, and B-cell activating factor are candidate mediators of spinal cord injury-induced autoimmunity. *J Neurotrauma.* 2013; 30:434–40. [PubMed: 23088438]
86. Savill J, Dransfield I, Gregory C, Haslett C. A blast from the past: clearance of apoptotic cells regulates immune responses. *Nat Rev Immunol.* 2002; 2:965–75. [PubMed: 12461569]
87. Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature.* 2007; 447:869–74. [PubMed: 17568749]
88. Schwab JM, Brechtel K, Mueller CA, Failli V, Kaps HP, Tuli SK, Schluesener HJ. Experimental strategies to promote spinal cord regeneration--an integrative perspective. *Prog Neurobiol.* Feb. 2006; 78(2):91–116. [PubMed: 16487649]
89. Schwab JM, Guo L, Schluesener HJ. Spinal cord injury induces early and persistent lesional P2X4 receptor expression. *J Neuroimmunol.* 2005; 163:185–9. [PubMed: 15885321]
90. Schwab JM, Frei E, Klusman I, Schnell L, Schwab ME, Schluesener HJ. AIF-1 expression defines a proliferating and alert microglial/macrophage phenotype following spinal cord injury in rats. *J Neuroimmunol.* Oct 1. 2001; 119(2):214–22. [PubMed: 11585624]
91. Schwab JM, Brechtel K, Nguyen TD, Schluesener HJ. Persistent accumulation of cyclooxygenase-1 (COX-1) expressing microglia/macrophages and upregulation by endothelium following spinal cord injury. *J Neuroimmunol.* 2000; 111:122–30. [PubMed: 11063829]

92. Schwartz M, Kipnis J. Therapeutic T cell-based vaccination for neurodegenerative disorders: the role of CD4+CD25+ regulatory T cells. *Ann N Y Acad Sci.* 2005; 1051:701–8. [PubMed: 16127010]
93. Serhan CN, Brain SD, Buckley CD, Gilroy DW, Haslett C, O'Neill LA, Perretti M, Rossi AG, Wallace JL. Resolution of inflammation: state of the art, definitions and terms. *FASEB J.* 2007; 21:325–32. [PubMed: 17267386]
94. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat Immunol.* 2005; 6:1191–7. [PubMed: 16369558]
95. Shen A. Immunological roles for axon regeneration receptors. *Exp Neurol.* 2014 this issue.
96. Soden RJ, Walsh J, Middleton JW, Craven ML, Rutkowski SB, Yeo JD. Causes of death after spinal cord injury. *Spinal Cord.* 2000; 38:604–610. [PubMed: 11093321]
97. Sroga JM, Jones TB, Kigerl KA, McGaughy VM, Popovich PG. Rats and mice exhibit distinct inflammatory reactions after spinal cord injury. *J Comp Neurol.* 2003; 462:223–240. [PubMed: 12794745]
98. Taranova NP, Makarov A, Amelina OA, Luchakova OS, Loboda EB, Leikin IB. [The production of autoantibodies to nerve tissue glycolipid antigens in patients with traumatic spinal cord injuries]. *Zh Vopr Neirokhir Im N N Burdenko.* 1992; 4-5:21–4. Russian. [PubMed: 1281366]
99. Teeling JL, Cunningham C, Newman TA, Perry VH. The effect of nonsteroidal anti-inflammatory agents on behavioural changes and cytokine production following systemic inflammation: Implications for a role of COX-1. *Brain Behav Immun.* 2010; 24:409–19. [PubMed: 19931610]
100. Uderhardt S, Herrmann M, Oskolkova OV, Aschermann S, Bicker W, Ipseiz N, Sarter K, Frey B, Rothe T, Voll R, Nimmerjahn F, Bochkov VN, Schett G, Krönke G. 12/15-lipoxygenase orchestrates the clearance of apoptotic cells and maintains immunologic tolerance. *Immunity.* 2012; 36:834–46. [PubMed: 22503541]
101. Vallières N, Berard JL, David S, Lacroix S. Systemic injections of lipopolysaccharide accelerates myelin phagocytosis during Wallerian degeneration in the injured mouse spinal cord. *Glia.* 2006; 53:103–13. [PubMed: 16206158]
102. Vargas ME, Watanabe J, Singh SJ, Robinson WH, Barres BA. Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. *Proc Natl Acad Sci U S A.* 2010; 107:11993–8. [PubMed: 20547838]
103. Wu B, Matic D, Djogo N, Szpotowicz E, Schachner M, Jakovcevski I. Improved regeneration after spinal cord injury in mice lacking functional T- and B-lymphocytes. *Exp Neurol.* 2012; 237:274–85. [PubMed: 22868200]
104. Wright BR, Warrington AE, Edberg DD, Rodriguez M. Cellular mechanisms of central nervous system repair by natural autoreactive monoclonal antibodies. *Arch Neurol.* 2009; 66:1456. [PubMed: 20008649]
105. Xu X, Warrington AE, Wright BR, Bieber AJ, Van Keulen V, Pease LR, Rodriguez M. A human IgM signals axon outgrowth: coupling lipid raft to microtubules. *J Neurochem.* 2011; 119:100–12. [PubMed: 21824142]
106. Zajarías-Fainsod D, Carrillo-Ruiz J, Mestre H, Grijalva I, Madrazo I, Ibarra A. Autoreactivity against myelin basic protein in patients with chronic paraplegia. *Eur Spine J.* 2012; 21:964–70. [PubMed: 22057439]
107. Zhang Y, Guan Z, Reader B, Shawler T, Mandrekar-Colucci S, Huang K, Weil Z, Bratasz A, Wells J, Powell ND, Sheridan JF, Whitacre CC, Rabchevsky AG, Nash MS, Popovich PG. Autonomic Dysreflexia Causes Chronic Immune Suppression after Spinal Cord Injury. *J Neurosci.* 2013; 33:12970–12981. [PubMed: 23926252]
108. Zhao P, Waxman SG, Hains BC. Modulation of thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia by cysteine cysteine chemokine ligand 21. *J Neurosci.* 2007; 27:8893–902. [PubMed: 17699671]

Figure 1. The CNS and immune system are integrated “supersystems” that regulate physiological homeostasis

The classical neuroimmunological perspective to research on SCI or other neurologic diseases has been to focus on leukocyte functions in brain and/or spinal cord, i.e., two immune-privileged sites. However, the modulatory effects of a CNS lesion on immune function were neglected (neurogenic immune ablation). For example, injury to the vegetative, sympathetic nervous system partly withdraws the control of the CNS on the immune and endocrine organs. Loss of this hardwiring has been designated as spinal cord injury-induced immune depression sndrome (SCI-IDS) and may increase the susceptibility to infection in a lesion height dependent manner and may also paradoxically promote autoimmunity. Non-neurogenic mechanisms of immune regulation including “systemic immune response syndrome” (SIRS) or “compensatory anti-inflammatory response syndrome” (CARS) are also elicited by injury and disease and likely increase incidence of infections. Infections are the major cause of death after SCI and have been identified as ‘disease modifying factor’ (DMF) characterized as independent risk factor for poor neurological recovery.

Differential resolution ability of leukocyte subsets to be cleared from the SCI lesion site (‘half life’)

Figure 2. ‘Defective’ resolution of inflammation after SCI

Resolution efficacy is measured as the number of cells being cleared from the lesion site. The cell-specific resolution interval R_i can be determined from the curve at the time when cell numbers decreased by 50% (data points represents the mean of $N = 5$). Several leukocyte subsets persist indefinitely implying that a ‘resolution-deficit’ exists after SCI. T-cell infiltrates plateau early with ~10% of maximal cell numbers remaining at chronic post-injury intervals. Macrophage and B-cell numbers decrease more slowly. Indeed, even several weeks post-injury, ~45% of maximal macrophage numbers persist (as can be predicted with reasonable certainty from nonlinear regression analysis) after SCI exemplified after a thoracic-level 8 SCI-Model in Lewis rats.

Figure 3. Hallmarks of CNS autoimmunity displayed by T - and B-Lymphocytes after SCI

A. T-lymphocytes are encephalitogenic after acute SCI. Pioneering reports were able to unravel that adoptive T cell transfer after SCI are encephalitogenic and able to breach in between the intact endothelium and cross the blood spinal cord barrier (BSB) to form classical infiltration clusters accumulating in the perivascular virchow-robin spaces as entry routes for invading T-cells (Popovich et al., 1996a). Permission for reprint will be requested.

B. B-lymphocytes form aberrant clusters and align along ectopic 'follicle-alike' structures in adjacent areas of the SCI lesion site and represent neuroimmunological hallmarks of a non-selflimiting inflammatory response after SCI. Remaining B-cell parenchymal clusters constitute a source of (auto-)antibody generation implied in degenerative complement mediated axonal damage but also autoimmune pathophysiology. Oligoclonal band synthesis has been reported after experimental SCI and in human CNS injury (A & B, 50 μ m).

Figure 4. Lesional and systemic maladaptive immune dysfunction after acute SCI is sustained and extends into the phase of chronic SCI

At the systemic level (*upper row*), initially after SCI the immune system is suppressed by ‘non-neurogenic’ (CARS/SIRS) and ‘neurogenic’ (SCI-IDS) mechanisms. With time after SCI, the imprint of SCI-IDS increases while the role of CARS/SIRS subsides in case of non-septic SCI-patients. The immune suppression facilitates the development of infections. Infections are the main cause of death in the acute and chronic phase after SCI and have been identified recently as an independent risk factor for poor neurological outcome in SCI patients.

(*Lower row*). In the injured spinal cord, sustained, non-resolving inflammation occurs and is associated with indices of neurodegeneration, demyelination and autoimmunity and neurologic changes associated with maladaptive plasticity (e.g., pain).

(*Middle row*). Systemic and localized (intraspinal) immune dysfunction are interdependent. SCI-IDS could be protective by limiting excessive autoimmunity against CNS-epitopes shielded behind the intact blood-spinal cord barrier (BSB). The penetrance of SCI-IDS is sufficient to prevent classical CNS autoimmune disease (e.g., MS) but is not sufficient for eliminating activation of B- or T cell autoimmunity (See also Table 1). Infections generate excessive host and pathogen-specific RNA, DNA and cell membrane detritus – all are immunogenic and act as adjuvants that are able to boost inflammation including the non-resolved inflammatory cascades active in the injured spinal cord. Moreover, conserved microbial structural motifs, referred to as pathogen-associated molecular patterns (PAMPs), are able to bind to cognate receptors grouped as Toll-like receptors (TLRs) (Akira et al., 2006), which are expressed by neuron, astrocytes, microglia, and oligodendrocytes. Infection derived ligand recognition by TLR is a candidate mechanism to directly foster neuronal injury, neurodegeneration, demyelination, autoimmunity and pain.

Table 1

Hallmarks and selected functionality/antigen specificity of natural autoimmunity and after spinal cord injury (SCI) ‘Naturally’ occurring autoimmunity and tissue maintenance

	Model	Serum/CSF	Functionality/proposed role
T cells			
<i>Characteristics (antigen...)</i>			
CD4, CD25, FoxP3 Tregs	Mouse		Neuroprotection and tissue homeostasis (for review see Schwartz and Kipnis, 2005; Beers et al., 2011)
CD8 > CD4	Rat		Immune surveillance (Bradl et al., 2005), preferentially grey matter
B cells			
<i>Characteristics (Ig-class, antigen...)</i>			
IgM			
β3-tubulin-reactive?	Mouse	recomb	propagated neurite outgrowth/stabilization (Xu et al., 2011)
	Mouse	S & CSF	propagated myelin clearance and regeneration (after PNS-injury) (Vargas et al., 2010)
Ganglioside-reactive Myelin-reactive	Mouse/Human		Remyelination, Neuroprotection, neurite outgrowth (for review see Wright et al., 2009)
Neuronal membrane reactive			
Regulatory B cells, MOG reactive (B10cells)	Mouse		Tissue homeostasis (e.g. Matsushita et al., 2010)
IVIG			
IgG unspecific, derived from healthy donors	Rat	Human	Immunomodulatory effect in human autoimmune disease (Gold et al., 2007) Neuroprotective in xenogenous application after compression SCI in rats (Nguyen et al., 2012).

Autoimmunity after SCI – Trauma-induced autoimmunity as a maladaptive, dysfunctional immune response and driver of neuropathology or suboptimal CNS repair

T cells				
	Model	Serum/CSF	Detection, Functionality/Role	
<i>Characteristic</i>				
MBP ₈₁₋₉₉ and MBP ₁₅₁₋₁₆₉ -reactive	human	S	n.d.	chronic SCI (Kil et al., 1999)
MBP-reactive	human	S	n.d.	chronic SCI, lesion severity dependent (Zajarias-Fainsod et al., 2012)
MBP-reactive	rat	S	n.d.	acute SCI – encephalitogenic (Popovich et al., 1996a) forming perivascular infiltrations (see also Fig. 3c)
MBP-reactive (MBP-TCR Tg)	mice		n.d.	increased secondary damage/demyelination impaired functional recovery (Jones et al., 2005)
<i>Functional assay</i>				
EAE-like symptoms	rat	S	n.d.	Adoptive T cell transfer after acute SCI leads to EAE-like disease with impaired locomotion and elevated EAE disease score (Popovich et al., 1996a)

B cells				
	Model	Serum/CSF		Detection
<i>Characteristic (Class, antigen)</i>				
IGM	Mice	S	n.d.	Acute SCI (form day 7 post SCI on) ELISA
IgG2a	Mice	S	n.d.	Subacute SCI (from day 14 post SCI on) ELISA
anti-DNA (ANA)	Mice	S	n.d.	‘Chronic’ SCI (6 weeks)

B cells				
	Model	Serum/CSF		Detection
anti-RNA	Mice	S	n.d.	'Chronic' SCI (6weeks)
anti-CNS	Mice	Sf	n.d.	'Chronic' SCI (6weeks) B-cells form ectopic parenchymal intraspinal lymphoid follicles juxtaposed to the lesion site (Ankeny et al., 2006, 2009, Kopp and Schwab, unpublished, see also Figure 3a).
anti-galactocerebroside (GalC)	Human	S	n.d.	Chronic SCI (Taranova et al., 1992)
anti-GM1 (IgG)	Human	S	n.d.	chronic SCI; (Hayes et al., 2002) associated with lesion severity (only in AIS A-C)
anti-GM1 (IgG)	Human	S	n.d.	associated with lesion severity, significantly enhanced in patients with infections such as UTI (Davies et al., 2007)
anti-MBP (IgG)	Human	S	n.d.	chronic SCI, lesion severity dependent (Zajarias-Fainsod et al., 2012)
Functional assay				
Reduced neurite outgrowth	Human	S	n.d.	Post-SCI sera on xenogen. neurons (Mizrachi et al., 1983)
Neurodegeneration	Mice	S	n.d.	Post-SCI sera injections in healthy brain (hippocampus) (Ankeny et al., 2009)
Impaired neurofunctional	ko-Mice	S	n.d.	Significantly improved hindlimb locomotion after SCI Neurological regeneration (Ankeny et al., 2009).

B and T cells			
	Model		Detection, Functionality/Role
Lacking functional	Mice	RAG2 ^{-/-}	Reduced demyelination (Wu et al., 2012).
T and B lymphocytes			Significantly improved hindlimb locomotion after SCI (Wu et al., 2012).