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Mechanisms and implications of adaptive immune responses after traumatic spinal cord injury

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Abstract

Traumatic spinal cord injury (SCI) in mammals causes widespread glial activation and recruitment to the CNS of innate (e.g., neutrophils, monocytes) and adaptive (e.g., T and B lymphocytes) immune cells. To date, most studies have sought to understand or manipulate the post-traumatic functions of astrocytes, microglia, neutrophils or monocytes. Significantly less is known about the consequences of SCI-induced lymphocyte activation. Yet, emerging data suggest that T and B cells are activated by SCI and play significant roles in shaping post-traumatic inflammation and downstream cascades of neurodegeneration and repair. Here, we provide neurobiologists with a timely review of the mechanisms and implications of SCI-induced lymphocyte activation, including a discussion of different experimental strategies that have been designed to manipulate lymphocyte function for therapeutic gain.

Keywords

autoimmune; lymphocyte; autoantibody; T cell; B cell; CNS injury

Introduction to adaptive immunity, lymphocyte regulation and autoimmune responses

General principles of lymphocytes and adaptive immunity

Cells of innate and adaptive immunity play fundamentally different roles during an immune response. Innate immune cells (e.g., neutrophils, monocytes, dendritic cells, etc.) provide immediate defense against infection or other inflammatory stimuli but also help activate and recruit cells of the adaptive immune system (i.e., T and B lymphocytes). This is accomplished through complex interactions involving antigen presentation and the release of various inflammatory mediators (e.g., cytokines and chemokines). Once lymphocytes recognize antigen, they proliferate, yielding large numbers of “daughter cells” or clones specific for that antigen (*clonal selection or clonal expansion*). Some clones persist indefinitely, providing “memory” against the inciting antigen. Childhood vaccines attempt to exploit this aspect of adaptive immunity by intentionally creating a persistent repertoire of lymphocytes with exquisite specificity for select pathogens (e.g., measles virus). More recently, therapeutic

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vaccines have been developed that try to exploit neuroantigen-specific T and B cell function for repairing the CNS (see below).

During an adaptive immune response, lymphocyte clones not entering the memory pool become effector cells which enter the circulation and home to sites of injury or infection in search of antigen. Therein, effector lymphocytes secrete cytokines and antibodies that orchestrate and amplify the functions of other immune cells. For example, when antibody binds to antigen, an immune complex is created that facilitates phagocytic removal of antigen. Antibodies also activate innate immune cells by cross-linking Fc receptors—specialized antibody receptors that have tyrosine-based activation motifs[2,16,101]. Immune complexes catalyze activation of serum and tissue complement—a system of proteins that circulate in the blood and are produced by glia and neurons in the CNS[5,11,29,74,126]. Activated complement proteins serve as chemotactic agents (e.g., C5a, C3b) to amplify immune cell recruitment and function and they can also directly lyse cells bearing target antigen. These *antigen-specific* immune responses will persist until the antigen is removed or until endogenous regulatory cascades suppress the response.

Originally, it was thought that each lymphocyte receptor was specific for a single antigen. More recently, it has become clear that a single T cell receptor (TCR) or immunoglobulin can bind epitopes found on a number of distinct antigens, i.e., they are *polyspecific*[37,132]. For example, a TCR or an antibody may be specific for a measles virus capsid protein but may also bind a protein present in CNS myelin. However, that same TCR or antibody might not bind skeletal muscle or *Mycobacterium tuberculosis*. Because the number of potential antigens far exceeds the number of lymphocytes found in the immune system, polyspecificity is important for optimal host-defense; however, it also introduces the potential for triggering autoimmunity.

Immunoregulation and autoimmunity

When lymphocytes recognize and become activated by self-antigens (e.g., non-pathogenic peptides, proteins, lipids or nucleic acids found in the host), autoimmune disease can develop. Due to the processes of receptor editing and positive and negative selection, most self-reactive lymphocytes are deleted or inactivated (*anergized*) during development. Why then do we maintain the ability to respond to self antigens throughout adulthood? Although the answer to this question is not entirely clear, there is compelling data to suggest that self-antigens are important for modulating the sensitivity of naïve lymphocytes and reducing the overall number of ligands needed to initiate an adaptive immune response[68,121]. In this way, autoimmune recognition plays a physiological role in adjusting the strength of the immune response. It is believed that autoimmune pathology occurs only after an ambiguous threshold of activation is surpassed in autoreactive cells. This likely requires an optimal but poorly understood interaction between antigen, antigen presenting cell and lymphocytes, with concomitant dysregulation of assorted immunoregulatory networks that maintain immunological tolerance (reviewed in[24]). For example, naturally occurring regulatory T cells (T_{regs}) suppress immune responses[23,65,90,115,118]. This suppression is antigen-specific, can be enhanced experimentally and is mediated by diverse mechanisms including the release of immune suppressive cytokines (e.g., TGFβ, see [1,13] for review). The fact that depletion of naturally occurring T_{regs} causes autoimmune disease in otherwise normal animals is evidence of the profound role for T_{regs} in maintaining immune tolerance[106,107].

Mechanisms of trauma-induced autoimmune disease: Lessons from Multiple Sclerosis

Despite the presence of multiple immune regulatory checkpoints, autoimmune disease does occur. Multiple sclerosis (MS) is the most common and best-understood CNS autoimmune

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disease. Like its primary animal model, experimental autoimmune encephalomyelitis (EAE), MS results when lymphocytes bind antigens on healthy myelin and axons causing demyelination and axon injury with the subsequent onset of neurological dysfunction[77]. Controversy surrounds the precise mechanism(s) responsible for triggering MS. The prevailing theory is that a viral infection activates polyspecific lymphocyte clones that also recognize CNS autoantigens[85,133]. In this scenario, lymphocytes that become activated by viral antigens bypass the blood-brain barrier where they become reactivated by myelin and/or axonal proteins that share sequence homology with the viral protein. Repeated exposure to the virus may trigger disease relapse in established MS[4].

Autoreactive lymphocytes also can infiltrate the CNS subsequent to BBB dysfunction caused by high levels of circulating cytokines released during infection or following idiopathic microvascular trauma[35,55,75,92,97,119,137]. Recent data also indicate dysregulation of T_{regs} in MS patients[102,128]. Once autoreactive lymphocytes bypass mechanisms of immune tolerance and gain access to the brain or spinal cord, they cause inflammation and cell death culminating in demyelination, axonal degeneration and neurological deterioration[56,127]. The autoimmune response is self-propagating and is characterized by recurrent BBB dysfunction with continued upregulation of molecules needed for T cell activation, i.e., MHC class II and costimulatory molecules on resident glia or infiltrating innate immune cells[45,46,50,58,63,78,100]. As a result of ongoing pathology, new CNS antigens are released that have the potential to ligate and activate other autoimmune lymphocytes [25,26,71,79,84]. This phenomenon is known as epitope spreading and can perpetuate neuroinflammation and pathological progression.

Obviously, the etiology of SCI and MS is different. However, there are some surprising commonalities (discussed below; also see Popovich et al.[94]) and in both cases, it appears that mechanisms of immunological tolerance are suppressed, resulting in the onset and maintenance of a chronic autoimmune response.

Autoimmunity induced by Traumatic SCI

Autoimmune reactions are triggered by traumatic SCI in animals and humans. In rats, SCI activates MBP-reactive T cells capable of causing neuroinflammation and transient paralysis[94]. In SCI humans, the frequency of MBP-reactive T cells increases, reaching levels that approximate those seen in MS patients[60]. Also, >50% of SCI patients have increased levels of serum and CSF antibodies specific for galactocerebroside, MBP and GM-1 gangliosides[43,86,123]. We have recently shown that CNS autoantibodies are significantly elevated in the circulation of >90% of SCI mice[6]. A preliminary analysis of potential autoantigen targets in SCI mice suggests that the breadth of autoimmune responses elicited by SCI extends beyond the predicted repertoire of neuroantigens (e.g., MBP) (Figure 1). Indeed, because SCI-induced autoimmune responses are so prevalent, it is logical to question how they are initiated and their pathophysiological significance.

Mechanisms of lymphocyte activation after SCI

Presumably, the trauma and vascular injury caused by SCI overcome mechanisms of peripheral tolerance and initiate the earliest phases of lymphocyte activation. This may occur subsequent to neuroantigens being released into the blood and lymphatics with drainage into spleen and lymph nodes[41,64,73]. Also, cells present in the injury site may sequester debris and carry CNS antigens to secondary lymphoid organs (spleen and lymph nodes) via these same humoral routes[54]. There, neuroantigens would be processed and presented by antigen presenting cells (e.g., dendritic cells) to lymphocytes, triggering lymphocyte activation. Support for peripheral priming of autoimmunity after SCI comes from our studies in mice showing that the number of activated T and B cells increases in the spleen and bone marrow within 24 hours of SCI[6,

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[53]. By three days, T cells isolated from secondary lymphoid tissues of SCI rats are capable of causing transient hind limb paralysis and spinal cord inflammation when they are injected *intravenously* into naïve recipients[94]. The pathogenic potential of SCI-activated B cells still remains to be directly tested, but early indications suggest that B cells also are pathological[6]. Data from other models also confirm a direct link between primary CNS pathology and peripheral lymphocyte activation[36,41,64,91].

Once lymphocytes gain access to the injury site, they persist indefinitely[6,59,110,120]. Indeed, T and B cell numbers increase in the mouse SCI lesion through at least 9 weeks post-injury. This occurs despite complete restoration of BBB integrity[17,93,129], suggesting that intraspinal cytokine/chemokine gradients exist chronically and are able to upregulate integrin expression on endothelia and nearby cells[9,12,70,80,109]. These chemokine gradients and adhesion molecules represent molecular targets for manipulating the effects of intraspinal lymphocytes after SCI[10,15,34,39,40]. The persistence or progressive increase in lymphocyte numbers may also be explained by lymphocyte reactivation and proliferation within the injured spinal cord. Indeed, intraspinal lymphocytes co-localize with parenchymal microglia, perivascular macrophages, infiltrating monocytes and B cells. All are cells that express the MHC class II antigens and costimulatory molecules (e.g., CD80, CD86) necessary for lymphocyte activation[6,59,95,96,108,120]. The presence of large T and B cell clusters in the injured spinal cord that are morphologically identical to germinal centers found in lymph node and spleen (sites of active lymphocyte proliferation and differentiation) further supports the hypothesis that cells are reactivated locally[6]. Similar “ectopic” lymphoid follicles have been described at sites of chronic autoimmune inflammation (e.g., synovium in rheumatoid arthritis, meninges in MS)[61,112,114]. Additional support for local activation comes from data showing intraspinal expression of genes encoding autoantibodies specific for systemic autoantigens (Fig. 1). Preliminary data suggest that potent lymphocyte survival/activation factors (e.g., APRIL or BAFF[81,135]) are expressed in the injured spinal cord (data not shown). The chronic expression of these factors could support autoimmune lymphocyte survival and function. As such, therapies designed to block these factors may prove beneficial by reducing the effects of post-injury autoimmunity. But regardless of why lymphocytes persist indefinitely at the lesion site, there is no doubt that these cells are uniquely positioned to influence post-injury degenerative and regenerative processes.

Functional implications of endogenous autoimmune responses triggered by SCI

Currently, the implications of post-traumatic lymphocyte activation and intraspinal accumulation remain ill-defined and controversial; what is known will be reviewed below. However, before considering if T and B cells exacerbate tissue injury or promote CNS repair, let us first consider which antigens are driving SCI-induced autoimmunity. By doing so, we hope to broaden the context in which the effects of T and B cells are considered after SCI.

In clinical and experimental SCI, only a few autoantigen targets have been documented (i.e., MBP, GM-1 ganglioside, galactocerebroside, glutamate receptor 2/3, RNA and DNA)[6,43,86,123] (also see Fig. 1). More recently, we used serum antibodies from individual SCI mice to probe homogenized spinal cord proteins separated by 2D-gel electrophoresis. A preliminary proteomics analysis of the 2D gels indicates that >50 different self-proteins are being targeted by SCI autoantibodies (data not shown). Because some of these autoantigens are found throughout the body (e.g., actin, RNA/DNA), it may be appropriate to consider SCI as a trigger for CNS *and* systemic autoimmune disease. For example, an increase in autoantibodies that bind nuclear antigens (e.g., RNA/DNA) and glutamate receptors[6] could cause or exacerbate renal insufficiency and may explain the idiopathic cognitive declines that occur in a subset of individuals with SCI[30,32]. Renal failure and reproductive sterility are considered to be

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secondary consequences of impaired neural function in para- or quadriplegics. However, it is intriguing to consider that autoimmune responses may contribute to this pathology[6]. Indeed, in patients with neuropsychiatric lupus, the polyspecific antibodies that bind DNA and NMDA receptors also cause kidney pathology and cortical neurodegeneration[31,67,125,130]. Antibodies with similar specificities are found after SCI in mice[6].

It is also possible that the autoimmune responses that we interpret as being CNS-specific are in fact aberrant byproducts of pre-existing host-defense reactions. For example, if an immune response against a bacterium or virus was occurring prior to SCI, activated polyspecific T and B cells could become reactivated in the inflammatory milieu of the injury site. In the same way that environmental pathogens trigger MS onset or disease relapses, pre- or post-traumatic exposure to pathogens or unrelated systemic trauma could initiate SCI-induced autoimmune reactions via polyspecificity.

Given that an alarming number of lymphocytes specific for pathogens or systemic antigens (e.g., nucleic acids) can also react with CNS antigens[3,18,31,37,49,51,72,124,130], it seems certain that SCI or any perturbation that can trigger an immune response will activate autoimmunity. However, there is little evidence that autoimmune processes cause delayed pathology or neurological decline after SCI or other forms of neural trauma (e.g., traumatic brain injury, stroke). Perhaps this is because the threshold for detecting these changes is extremely high after severe CNS injury. Indeed, in an individual who is already paralyzed, it would be difficult to discriminate a neurological deficit resulting from focal activation of T or B cells in discrete regions of the spinal cord. Alternatively, because researchers and clinicians typically focus on measuring changes in spinal-mediated motor/sensory function (both after SCI and in MS), it is possible that pathology caused by autoimmunity in systemic organs (e.g., kidney) or disturbances in cognitive function would be missed or simply attributed to neural deficits caused by SCI. An equally plausible explanation is that severe trauma activates immunoregulatory pathways that limit the extent of autoimmune pathology. For example, studies by Lafaille and colleagues showed that SCI simultaneously activates T_{regs} and pathogenic autoreactive T cells. In this model, T_{regs} were shown to control and arrest pathogenic T cells thereby limiting inflammation and injury-induced gliosis[14,19,90,136]. Interestingly, in transgenic mice deficient in T_{regs}, SCI induces pathological autoimmunity[53,69]. Injury-induced suppression of pathological autoimmunity may also be a consequence of dysregulated function in the sympathetic nervous system and neuroendocrine axis. We and others have shown that circulating levels of glucocorticoids are increased and that norepinephrine-mediated killing of lymphocytes is enhanced after SCI and stroke[27,28,66,76,99]. The resulting lymphocyte death could simultaneously limit the potential for developing autoimmunity while simultaneously increasing susceptibility to opportunistic infection.

Finally, we must consider the possibility that some autoimmune reactions are tolerable and may in fact be beneficial. For example, autoimmune cells including those reactive with MBP have been shown to secrete neurotrophins like BDNF upon stimulation by antigen[33,47,57]. This is thought to protect CNS cells from degeneration and also may promote axon growth and repair [87,116]. Because autoimmune cells selectively accumulate in and nearby sites of CNS injury, neurotrophins may be delivered in a context-dependent manner. The potential benefits afforded by autoimmune reactions after CNS injury are discussed in more detail below.

Manipulating adaptive immunity as a therapy for SCI

Clearly, the adaptive immune system is capable of exacerbating tissue damage and promoting various indices of CNS repair. A focus of current research is to learn how to exploit

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autoimmune-mediated repair while minimizing or circumventing the pathological consequences of autoreactive lymphocytes. A few of these approaches are summarized below.

Strategies seeking to enhance adaptive immunity for repair of injured spinal cord

Numerous studies have intentionally evoked autoimmune responses after SCI using active immunization or vaccine protocols (i.e., where antigens emulsified in immune-stimulating adjuvants are injected into the injured subject). Huang et al. immunized SCI mice with whole spinal cord homogenate in an attempt to promote axon regeneration[48]. The goal of this study was to increase the production of autoantibodies that would bind proteins in myelin known to inhibit axon growth (e.g., MAG). Indeed, only in immunized mice were anti-myelin antibody titers increased concomitant with enhanced axon regeneration beyond the site of SCI[48]. A similar approach was used to successfully block the axon growth-inhibitory properties of Nogo-A[83]. Specifically, an intrasplenic injection of a fusion protein containing the NogoA peptide was used to promote synthesis of high-affinity anti-Nogo-A antibodies. Importantly, this immunization protocol rapidly increased anti-Nogo-A antibodies without inducing pathological autoimmunity[83]. Schwartz and colleagues have shown that autoantigen vaccines can also safely induce T cell-mediated neuroprotection, i.e., "protective autoimmunity" [42, 62,88,113].

As an alternative to active immunization, the passive delivery of autoantibodies has been used successfully as a repair strategy in models of demyelination, Alzheimer's disease and SCI[8, 38,111]. Rodriguez and colleagues discovered an IgM autoantibody that binds to oligodendrocyte precursor cells and stimulates their entry into the cell cycle *in vitro*[103,104]. When injected *in vivo*, these antibodies promote remyelination of chemically-demyelinated spinal cord lesions[105]. In models of SCI, Schnell et al. showed that infusions of IN-1 antibodies, later shown to bind Nogo, stimulated long distance axon growth and functional recovery[22,82,111]. The repeated successes using IN-1 and later generation anti-Nogo antibodies to promote axon regeneration and functional recovery in rodents and primates has resulted in the start of a Phase I clinical trial in which humanized anti-Nogo antibodies are being tested as a treatment for human SCI[20,21].

Evidence that suppressing adaptive immunity is neuroprotective after SCI

Using vaccine protocols similar to those described above, we and others have shown that autoimmune responses can exacerbate CNS pathology[7,36,52,89,122,131]. In fact, when used in rat and mouse models of peripheral or CNS injury, active and passive immunization protocols consistently exacerbate neuropathology and impair neurological function[7,52]. Surprisingly, autoimmune vaccines caused a disseminated experimental autoimmune attack (i.e., EAE) throughout the neuraxis in mice receiving a facial nerve axotomy[7]. Importantly, no disease developed in immunized mice not receiving a peripheral nerve injury[7]. These data emphasize the potential for mild nerve injury to break or overcome mechanisms of immune regulation in the periphery.

In a separate study, we performed SCI in mice possessing a T cell repertoire biased towards recognition of MBP[53]. We predicted that these mice would reveal the true physiological potential of MBP-reactive T cells in the context of SCI. Indeed, without using adjuvants to bias the function T cells, we could examine how neuroantigen-specific T cells influence, in a context-dependent fashion, neuropathology and recovery from SCI. If MBP-reactive T cells are neuroprotective as predicted by the concept of protective autoimmunity, then we expected that T cell activation and entry into the spinal cord would reduce demyelination and axonal injury and promote functional recovery. Conversely, if they augment the acute destructive potential of innate immunity and exacerbate antibody-mediated demyelination and axonal injury, we predicted that spinal cord pathology and associated neurological deficits would be

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enhanced. The data clearly support the notion that MBP-reactive T cells are neurodestructive in the context of a sterile SCI[53].

Other data also suggest that lymphocytes are deleterious to the injured CNS. For example, SCI mice given antibodies against CXCL10, a chemokine which facilitates T cell recruitment to sites of inflammation, had reduced T cell accumulation accompanied by significant anatomical and functional preservation[40]. Similarly, when rats devoid of T cells (athymic nude rats) received a SCI, the lesions were significantly smaller and functional recovery was improved relative to SCI rats with T cells[98]. However, using a model of facial nerve axotomy, Jones and colleagues have shown that survival of axotomized motor neurons depends on the presence of an anti-inflammatory $CD4^+$ T cells[30,117]. More recently, this same group expanded their analysis of T cell subsets influenced by axotomy and showed that both anti-inflammatory (Th2 or T_{regs}) and proinflammatory (Th1 or Th17) T cells were activated [134]. This balanced activation of different T cell subsets may be important for T cells to exert a neuroprotective phenotype. Interestingly, after SCI, adaptive immunity is biased towards the Th1 proinflammatory phenotype[6,53]. Thus, the preferential induction of Th2 immunity may prove to be neuroprotective after SCI[44]. More studies are needed to prove this conclusively.

Conclusions

There is compelling evidence that SCI activates autoreactive T and B cells with the potential to exert divergent functions. On the one hand, studies have shown that endogenous autoimmunity can be enhanced to promote spinal cord repair. On the other hand, there are data that prove that autoimmune responses can exacerbate the deleterious consequences of spinal cord or peripheral nerve injury. From these conflicting data, it is becoming clear that in order to develop safe and effective therapies, we must learn how to simultaneously suppress the pathological effects of lymphocytes and boost their reparative effects without interfering with their pivotal role in host-defense. The challenge for the future is to reveal the key molecular determinants that control these divergent functions. Only then can we make treatments like this a reality.

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Abbreviations

SCI

Spinal cord injury

CNS

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	Central nervous system
TCR	T cell receptor
T_{reg}	Regulatory T cell
MS	Multiple Sclerosis
EAE	Experimental autoimmune encephalomyelitis
BBB	Blood-brain barrier
MBP	Myelin basic protein
CSF	Cerebrospinal fluid

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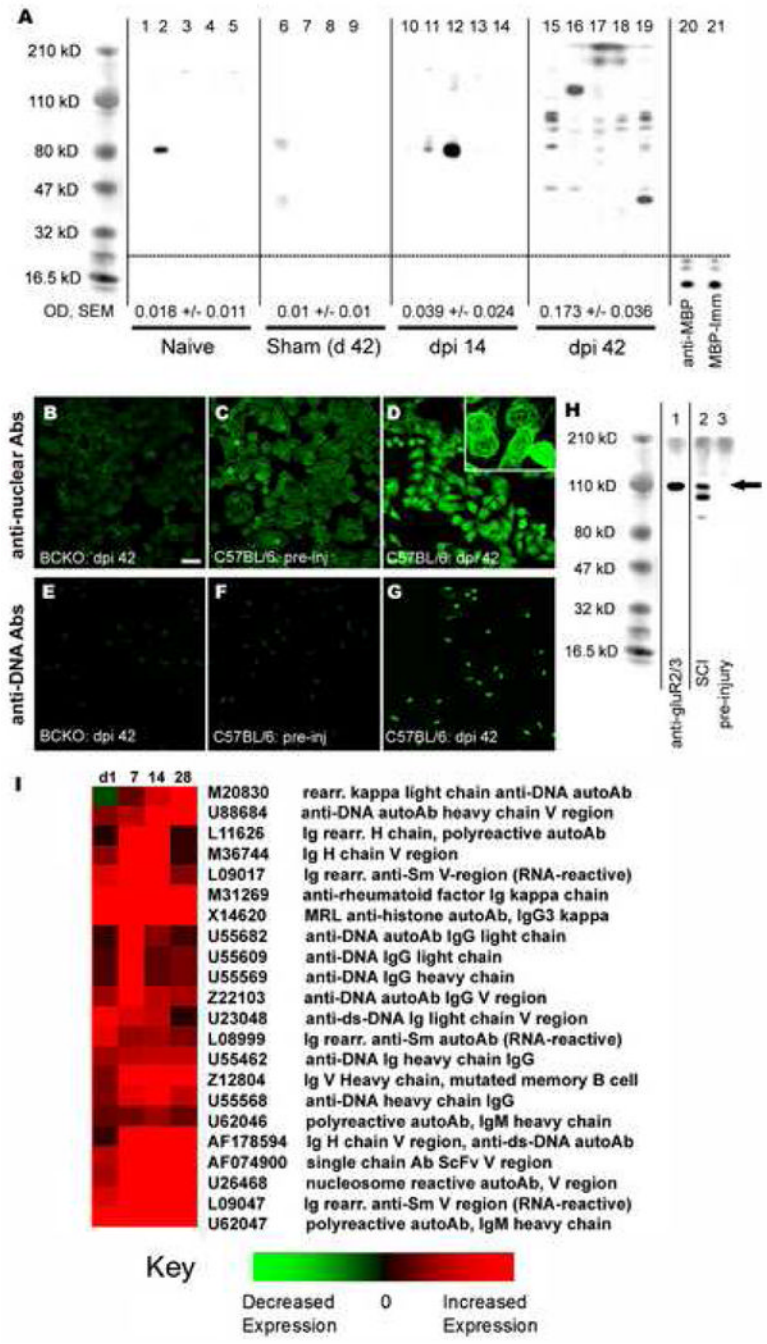

Figure 1.

SCI triggers production of antibodies specific for systemic and CNS antigens. (A) Sera from naïve (n=5; lanes 1-5), sham (n=4; lanes 6-9) or SCI mice at 14 (n=5; lanes 10-14) or 42 days post-injury (n=5; lanes 15-19) were used to probe homogenized CNS proteins. Lane 20 was probed with a commercial anti-MBP antibody (1:40,000) and lane 21 with serum (1:200) from a mouse immunized 35d previously with 200 μg guinea-pig MBP in adjuvant. Quantitation of mean band intensity in each lane within a group is shown and reveals marked induction of anti-CNS antibodies at 42 dpi vs. naïve, sham and 14 dpi groups (*OD ± SEM at the bottom of each column; *** p< 0.001 vs naive, **p < 0.01 vs sham, *p < 0.05 vs dpi 14, ANOVA with Tukey's post test; mean binding in samples from sham or uninjured mice were not different from zero;*

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t-test). (B-G) Sera were used to probe HEp-2 (B-D) and Crithidia luciliae (E-G) substrate slides (for anti-nuclear and anti-DNA antibodies, respectively). Sera from SCI B cell knockout (BCKO, B&E) and uninjured (C&F) mice fail to show anti-nuclear or anti-DNA binding. In contrast, sera from SCI C57BL/6 mice (D&G) reveal strong binding to nuclear antigens and DNA. High power (inset in D) shows labeling consistent with binding to nuclear membranes, nucleosomes and/or centromeres. (H) Sera from SCI mice indicate possible binding to neuronal glutamate receptors [~110 kD; compare anti-GluR2/3 positive-control labeling (lane 1) with SCI (dpi 42) sera labeling in lane 2]. Pre-injury sera failed to bind neuronal antigens (lane 3; arrow). *Scale = 25 μm (B-G)*. (I) Gene chip data shows upregulation of selected genes encoding autoreactive immunoglobulins within the mouse SCI contusion site. Data are expressed relative to genes found in the spinal cord of mice given laminectomy (sham) surgery but no SCI. (A-H reprinted with permission from The Journal of Neurochemistry, November 2006, Volume 99(4), pg 1073-1087.)